The first conference on **ACTH**
was sponsored by ARMOUR & COMPANY, Chicago,
and held at the Hotel Stevens, Chicago,
on October 21 and 22 1949

Proceedings of the First

Clinical ACTH

Conference

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Introduction

This volume constitutes the Proceedings of the First ACTH Conference held in Chicago on October 21 and 22 1949 under the auspices of Armour and Company

The following information is an outline of the events which led to calling the Conference which has resulted in this volume being published

In the Fall of 1946 The Armour Laboratories made available a preparation of ACTH (Adrenocorticotrophin) to ascertain the properties of this hormone in the human being Dr George W Thorn and his colleagues were the first to study this preparation and found that it *produced certain physiologic and metabolic effects* Shortly *thereafter* Dr Fuller Albright and his colleagues used the preparation and confirmed Dr Thorn s observations

During the succeeding two years the effect of stimulating the adrenal cortex with ACTH (Armour) was studied in normal human beings and individuals with obvious endocrine defects by a number of investigators among whom may be mentioned J S L Browne and his associates Sayers and Burns Lawson Wilkins and Roger A Lewis Jerome W Conn Randall G Sprague and Harold L Mason Allan Kenyon and Richard Landau Nathan B Talbot J W Jailer and his colleagues Robert F Loeb and his associates and Hoagland and Pincus

Practically all of these studies were metabolic balance studies designed to obtain a maximum amount of information concerning adrenal cortical function from the very limited supply of ACTH which was available As a consequence a substantial body of information has been accumulated concerning the physiologic and metabolic effect of stimulating adrenal glands in normal human beings and individuals with obvious endocrine defects

During this first two year period two disease syndromes in which there may be a metabolic defect were studied namely myasthenia gravis and gout the first by Soffer and the second by Conn Hellman and Wolfson These investigators found that the clinical status of the patient was materially altered as a result of adrenal cortical stimulation by ACTH (Armour)

During the latter portion of this first two year period a number of groups were exploring the metabolic function of the adrenal cortex in what were called at the time miscellaneous diseases but there was

no thought at the time that stimulation of the adrenal cortex by ACTH (Armour) would alter the clinical course of any of the syndromes under investigation However definite improvement was observed by several investigators in several diseases under the conditions of the acute experiments being done

In December 1948 Dr Edith B Farnsworth requested ACTH to study the effect of adrenal cortical stimulation in nephrosis in which she hypothesized a metabolic defect in adrenal cortical function, and found in fact that the clinical status of the nephrotic patient was substantially altered as a result of the hormone administration

In the latter part of January 1949, Dr Philip Hench requested ACTH to study adrenal cortical function in rheumatoid arthritis in line with his hypothesis that there may be an adrenal cortical defect underlying this disease The results observed are, of course, now widely known

The obvious extension of Dr Hench s observations was to study the effect of adrenal cortical stimulation in the so called "collagen diseases" which was done by several groups among whom may be mentioned Hench, Thorn Massell Howard Stokes Ragan and Bauer

However it was obvious that something fundamental in human physiology had been encountered in view of the fact that the clinical status of patients was substantially altered when the adrenal cortex was stimulated in such widely divergent syndromes as myasthenia gravis gout nephrosis and rheumatoid arthritis

In consequence the decision was taken to keep the studies on a broad base to ascertain the range of diseases that may be altered by adrenal cortical stimulation In fact every attempt has been made to meet the requirements insofar as supplies permit of any group who has desired to study the effect of adrenal cortical stimulation in any disease which has not been previously studied, provided the group concerned has had the personnel and facilities available to undertake metabolic balance studies or other objective control of a comparable character This was necessary in order that a maximum amount of information can be accumulated concerning adrenal cortical function in different disease states This screening of disease syndromes is in fact still in progress

By the Fall of 1949 a large number of groups had observed in a preliminary fashion the results of adrenal cortical stimulation in a wide variety of diseases However no one group knew either the number of groups working or the variety of disease syndromes under investigation There were in consequence a number of rumors abroad involving both information and mis information concerning the effect

of adrenal cortical stimulation in various disease syndromes In view of this situation several investigators suggested that it might be constructive to hold a Conference between all of the investigating groups in order that information and data could be exchanged between all of the groups working on the problem to the end that everyone working in this field of medical research could have a clearer picture of the overall problem confronting them

The Armour Laboratories agreed to call a Conference in Chicago on October 21 and 22 1949 on behalf of all of the investigators to permit this exchange of information

It was obvious to everyone concerned that all the data presented could be only preliminary and tentative since insufficient time had elapsed and inadequate supplies of the hormone had been available to any one group to allow any final or valid conclusions to be reached

There were 52 papers presented in this two day period and the rules of the Conference were that each speaker was limited to 10 minutes and each discussor to 3 minutes Discussion was encouraged in order to allow a maximum exchange of information but points made by discussors were to be covered by the presentation of factual data In fact the major objective of the Conference was to attempt to arrive at the best possible overall factual picture of adrenal cortical function in normal human beings and patients ill with various disease syndromes

The Conference attendance was limited to actual investigators and their associates and was maintained at the most informal level possible in order that the greatest exchange of information could be achieved

The rules of the Conference also stated that a complete transcript of the Conference would be made and that the manuscripts and discussion would be printed and bound for the members of the Conference

After the Conference all manuscripts and discussion transcripts were returned to the contributors for revision in the light of what was learned at the Conference The original plan was to have the manuscripts and transcripts in the hands of the contributors in three days and to have the final manuscripts and discussion transcripts ready for printing within three weeks after the Conference

However the discussion was so extensive that three weeks were required to complete its transcription Furthermore as often happens at such an informal conference many contributors undertook revision of their manuscripts and discussion transcripts to the end that a considerable delay occurred

Since the major value of this volume is early availability of the information contained herein the decision has been taken to publish the manuscripts and discussion as they were returned to the editor

without further editing or correction by the author the editor or the publisher

In view of the fact that this volume is nothing more than the proceedings of an informal conference we believe that early availability of the information far outweighs the delay that would occur if the manuscripts were further edited and corrected by the editor, the author and the publisher We believe that any errors that may be found in this volume are minor since each contributor has had an opportunity to correct his manuscript and the transcript of his discussion before printing

It must be realized that this Conference is nothing more than a status report of the projects in progress at the time, and in no case are any of the results presented to be considered finally valid or conclusive In consequence no contributor to this volume may be quoted without the prior permission of the contributor

It is clear from the data contained herein that adrenal cortical function is involved in a large number of disease syndromes and it may be said that the number of disease syndromes concerned has in fact already extended well beyond those listed in this document

Furthermore, it is obvious that a tremendous amount of work will be required not only to arrive at valid conclusions concerning the effect of adrenal cortical stimulation in various disease syndromes, but, more important to elucidate the physiologic and metabolic abnormalities which may be concerned in these various disease states

In summary this document represents the Proceedings of the First ACTH Conference which was held to clarify insofar as possible, the thinking with respect to the role of the adrenal gland in health and disease and to allow a re orientation of thinking with respect to this subject No information in this volume may be considered to be conclusive until it has appeared in the various technical publications in final form

All of the ACTH used in the studies in this volume is that produced by the Armour Laboratories except where otherwise specified

JOHN R MOTE

Chicago
February 1950

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1

Eosinophil Observations in Adrenocorticotrophic Hormone (ACTH) Therapy

Theron G Randolph and John P Rollins

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL CHICAGO

Serial observations of the circulating eosinophils have been made prior to and following adrenocorticotrophic hormone (ACTH Armour) in 24 cases of rheumatoid arthritis bronchial asthma allergic rhinitis and other allergic diseases

The technique employed in enumerating eosinophils was described by one of us (T G R) in 1943 and 1944 [1] [2] It consists of a diluting fluid containing methylene blue and phloxine dissolved in equal parts propylene glycol and water which permits the enumeration of eosinophils in the same counting chamber specimen employed in counting the total leucocytes In this medium the granules of the eosinophil stain brilliant red and the limiting membranes of all white blood cells remain intact in contrast to ruptured or ghost eosinophil forms of the Dunger [3] technique or the modifications thereof [4] In our experience [6] or that of Henneman Wexler and Westenhaver [7] the glycol stain technique is the most accurate method of estimating the number of eosinophils per cu mm of blood

It should be pointed out that the counting chamber method employed permits the chamber differentiation of mononucleated elements from polymorphonuclear leucocytes In addition it is also possible to differentiate young myeloid cells having indented nuclei as observed in acute allergic reactions following the experimental ingestion of allergenic foods or drugs [9]

The major steps in the glycol stain technique are shown in Fig 1

Fig 2 illustrates the variations in circulating eosinophils and other cellular elements occurring in a patient with allergic rhinitis headaches gastro intestinal symptoms and the fatigue syndrome of allergic origin [10] One should note the initial leucopenia occurring at one hour followed by the development of a marked leucocytosis lymphopenia

and progressive eosinopenia The initial transient leucopenia occurring after the administration of ACTH, although observed by Dougherty and White,[11] is apt to be missed if blood counts are not taken more frequently than once in 4 hours following the injection It may be seen that the eosinophils disappeared from the peripheral blood 3 hours after the intramuscular injection of 25 0 mgm ACTH

THE COUNTING CHAMBER DIFFERENTIATION OF
EOSINOPHILS WITH GLYCOL STAIN DILUTING FLUID

STOCK SOLUTIONS

0 1 PER CENT METHYLENE BLUE IN PROPYLENE GLYCOL	0 1 PER CENT PHLOXINE IN PROPYLENE GLYCOL

WORKING SOLUTIONS

DILUTE ABOVE STOCK SOLUTION WITH AN EQUAL AMOUNT OF DISTILLED WATER	DILUTE ABOVE STOCK SOLUTION WITH AN EQUAL AMOUNT OF DISTILLED WATER

FINAL STAIN

MIX AN EQUAL NUMBER OF DROPS OF
THE TWO WORKING SOLUTIONS PRIOR TO USE AS
WHITE BLOOD CELL DILUTING FLUID

FIG 1

The eosinophils reappeared at 6 hours and again disappeared 2 hours after a second injection of the same amount It is of further interest that the increment increase of the total leucocyte count consisted entirely of myeloid elements including many younger forms These blood variations following the administration of ACTH to human subjects were first described by Hills Forsham and Finch [12] and by

Hellman[13] We have been impressed by the fact that identical serial blood changes have been observed to follow the experimental ingestion of allergenic drugs in specifically sensitized patients[9]

The disappearance of the eosinophils from the circulating blood within the first 24 hours of ACTH therapy is arbitrarily considered as an immediate eosinophil response this occurred in 12 short courses of

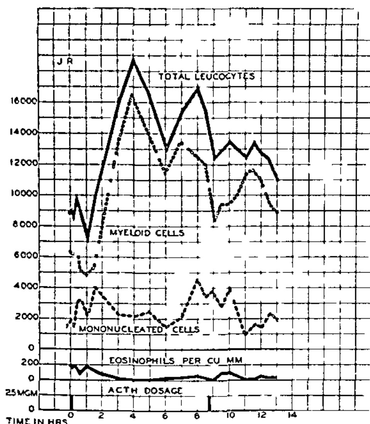


Fig 2

adrenocorticotrophic hormone therapy in 9 patients as summarized in Fig 3

An immediate eosinophil response also occurred in 9 individuals receiving long term ACTH treatment as shown in Fig 4 Three of these patients having an initial eosinophil level of less than 100 cells per cu mm developed edema during the first week of therapy although two of them received only a total daily dose of 60 0 mgm and the third 100 0 mgm of ACTH In each instance the clinical evidence of edema disappeared with a reduction in dosage

When a period longer than 24 hours was required for the disappearance of eosinophils from the circulating blood an arbitrary classification of a delayed eosinophil response was made This occurred in 5

PATIENT	AGE	SEX	EOSINOPHILS PER CU MM PRE TREATMENT	EOSINOPHILS PER CU MM 24 HOURS AFTER ACTH	INITIAL DOSE IN MGM	DAILY DOSE IN MGM	THERAPY IN DAYS	TOTAL ACTH IN MGM
C P I	43	M	1 087	0	25	100	2	225
P B	31	M	484	0	50	150	2	350
E O I	50	F	418	0	25	100	2	225
A S I	76	M	385	0	25	100	3	325
E O II	50	F	374	0	25	100	2	225
J R II	32	F	220	0	25	50	½	50
A S II	76	M	209	0	25	100	2	225
H D	50	F	209	0	25	100	2	225
M S	38	F	55	0	25	100	3	325
J R I	32	F	44	0	33	33	1	33
L I	68	M	33 &	0	16	50	2	125
M A	38	F	22	0	25	100	1	125

& OVER TREATED AS EVIDENCED BY THE DEVELOPMENT OF EDEMA

FIG 3 The immediate eosinophil response in short term ACTH treatment

PATIENT	AGE	SEX	EOSINOPHILS PER CU MM PRE TREATMENT	EOSINOPHILS PER CU MM 24 HOURS AFTER ACTH	INITIAL DOSE IN MGM	DAILY DOSE IN MGM	AVERAGE DAILY DOSE IN MGM	THERAPY IN DAYS	TOTAL ACTH IN MGM
J S	56	M	626	0	10	40	41	115	4 766
M N	69	F	308	0	25	100	60	43	2 580
A U	35	F	297	0	25	100	64	32	2 050
M H	64	F	253	0	15	60	40	23	920
H A	32	F	143	0	25	100	41	46	1 870
B L	42	M	99 &	0	25	100	57	36	2 060
R L	42	M	77 &	0	15	60	26	69	1 800
C F	53	F	44	0	25	100	56	39	2 170
M G	45	F	33 &	0	15	60	38	33	1 250

& OVER TREATED AS EVIDENCED BY THE DEVELOPMENT OF EDEMA

FIG 4 The immediate eosinophil response in long term ACTH treatment

individuals receiving a short course of ACTH therapy as illustrated in Fig 5

A similar delayed eosinophil response also occurred in 2 patients receiving long term therapy as summarized in Fig 6 A patient with rheumatoid arthritis exhibiting a typical cellular response of this type is shown in Fig 7

EOSINOPHILS PER CU MM

PATIENT	AGE	SEX	*PRE TREAT MENT*	*24 HOURS AFTER ACTH*	*48 HOURS AFTER ACTH*	*INITIAL DOSE IN MGM*	*DAILY DOSE IN MGM*	*THERAPY IN DAYS*	*TOTAL ACTH IN MGM*
C P B	43	M	1 540	55	0	25	100	2	225
B H	38	F	1 064	286	55	25	100	2	225
R F	6	M	836	308	88	16	50	3	225
R K	9	M	352	187	22	8	25	3	140
D S	42	F	275	22	0	25	100	2	225

Fig 5 The delayed eosinophil response in short term ACTH treatment

EOSINOPHILS PER CU MM

PA TIENT	AGE	SEX	PRE TREAT MENT	24 HOURS AFTER ACTH	48 HOURS AFTER ACTH	INITIAL DOSE IN MGM	DAILY DOSE IN MGM	AVER AGE DAILY DOSE IN MGM	THERAPY IN DAYS	TOT ACTH IN MGM
E B	34	F	495	319	55	15	60	55	58	3 165
R C	50	M	396 &	209	352	25	100	175	20	3 500

& UNDER TREATED AS EVIDENCED BY FAILURE TO RELIEVE SYMPTOMS HE LATER RESPONDED TO HIGHER DOSAGE

Fig 6 The delayed eosinophil response in long term ACTH treatment

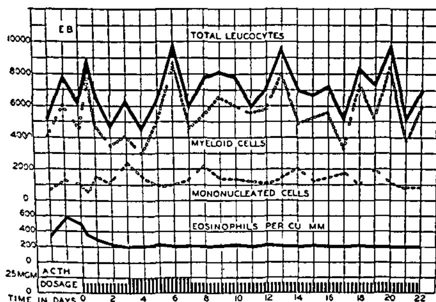


Fig 7

SUMMARY AND CONCLUSIONS

1 An intramuscular dose of ACTH sufficient to affect the level of circulating eosinophils results in the greatest degree of eosinopenia between 3 and 5 hours after the injection

2 Eosinophils may disappear from the circulating blood in patients treated with ACTH irrespective of the level of the preexisting eosinophil count

3 Patients with low eosinophil counts that is less than 100 cells per cu mm of blood are prone to develop over dosage phenomena In our experience such patients should not be given a larger initial dose than 25 0 mgm and preferably not more than 75 0 mgm during the first 24 hours of therapy

4 The sustained absence of eosinophils in the peripheral blood during the first 24 hours of ACTH administration either accompanies adequate dosage as judged clinically or it may be one of the first warnings of over dosage as the latter occurs prior to the development of edema or other clinical evidence associated with over dosage It is recognized however that under certain circumstances fluid retention to the point of edema may not reflect over dosage

5 The failure of eosinophils to diminish markedly or to disappear from the peripheral circulation during the first 24 hours of ACTH therapy is commonly associated with a clinically inadequate therapeutic response This finding may be regarded as suggestive evidence of under dosage or of some inadequacy of the function of the pituitary adrenal system

6 In the presence of unimpaired adrenal function an injection of ACTH is not only followed by an eosinopenia but is also accompanied by an initial transient leucopenia a subsequent leucocytosis associated with a shift to the left of the constituent myeloid elements and a lymphopenia

7 Although variations in the eosinophil level may occur in continued ACTH therapy frequent blood eosinophil observations are helpful in appraising the adequacy of dosage in sustained treatment

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DISCUSSION

DR GEORGE W THORN Dr Randolph s paper raises several interesting points I would hesitate to have this group gain the impression that one would adjust the dosage of ACTH on the basis of the initial blood eosinophil count In certain patients such as those with disseminated lupus there may be no eosinophils at all and yet one must start often times with a dose of 100 mgs of ACTH per day I think Dr Randolph s point about using the eosinophil count as a measure of the adequacy of therapy is very useful in most patients We all recognize that there are limitations to this indicator system but, in general it is

2 Eosinophils may disappear from the circulating blood in patients treated with ACTH irrespective of the level of the preexisting eosinophil count

3 *Patients with low eosinophil counts that is less than 100 cells* per cu mm of blood are prone to develop over dosage phenomena In our experience such patients should not be given a larger initial dose than 25 0 mgm and preferably not more than 75 0 mgm during the first 24 hours of therapy

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worsening of the disease as manifested by symptomatology, signs and an elevation of the ESR

We have been at loss to explain this escape phenomenon We have considered this phenomenon to have been allergic in origin However, the uric acid creatinine ratio determinations in 3 patients who have shown this phenomenon have not been adequately decreased Two showed a decrease of 16% and 17% respectively while the third showed an increase of 18% in the ratio This fact is against an explanation by allergic mechanisms

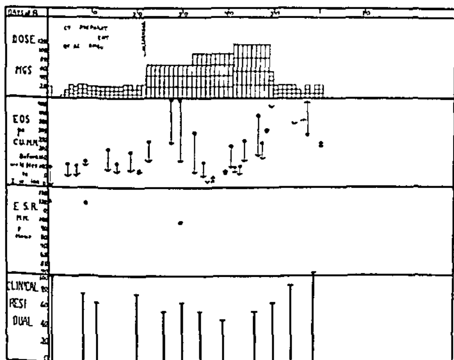


FIG 9 G S ♀ 56 Rheumatoid arthritis severe 13 years

A second explanation of the failure of eosinophile response is the theory that the adrenals have become either fatigued blocked or refractory to stimulation to ACTH in a dosage which was formerly effective

Have other workers noted this phenomenon? May the explanation be that the adrenals after a period of adequate response become incapable of response unless the stimulus is increased?

DR PETER H FORSHAM We have had a number of similar experiences which one might call escape from ACTH There are two possibilities

very helpful clinically as a measure of the adequacy of therapy or the capacity of the adrenal cortex to respond

DR WALTER BAUER We agree with Dr Thorn

DR CHESTER H ADAMS (Hospital for Special Surgery New York City) Dr Randolph has shown that there is a marked lowering of the number of circulating eosinophiles following the injection of ACTH into individuals with normally functioning adrenals This fact has been

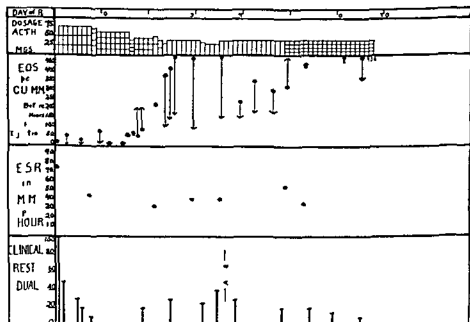


FIG 8 F S † Rheumatoid arthritis severe 5 months

used as a test of adrenal function and to measure stimulation of adrenals by injected ACTH

In patients with rheumatoid arthritis we have noted the eosinophile response described and we have used this as a test of adequate ACTH dosage and adequate adrenal response In general the clinical course of the disease as manifested by symptoms objective findings and sedimentation rate has closely followed the eosinophile response

We have however noted in several cases two of which are illustrated by the following charts that there is a period roughly 20 to 30 days following the initiation of ACTH administration when the eosinophile response decreases and later even fails even though the amount of ACTH administered is unchanged At this time there is a

shake only 30 times, smoothly and never let eosinophils or the cells stand in the diluting fluid for any length of time one will have results which are entirely analogous to those obtained by Dr Randolph's method and its slight modification by Henneman, et al

What are the advantages and disadvantages? One advantage of the acetone eosin method is that it is rapid One draws the blood into the pipette and dilutes immediately shakes 30 times plates and then counts In methods using the phloxine propylene diluent, however one has the great advantage of being able to leave the blood in the

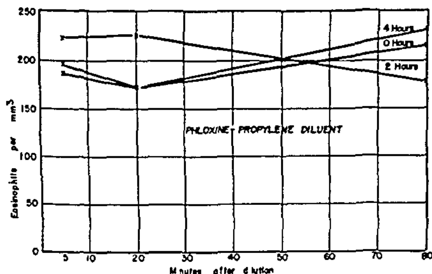


FIG 11 Circulating eosinophil counts performed at 3 time intervals after dilution showing lack of significant change in counts with passage of time and aging of oxalated blood (Fig 2 Henneman Philip H Wexler Hilda and Westenhaver Mary M A comparison of eosin acetone and phloxine propylene glycol diluents in eosinophil counts *Jour Lab & Clin Med* 34 1019 July 1949)

pipette for any number of hours which means that it makes it much easier for clinical work but when it comes to the counting one has to shake a little bit longer and then wait at least 15 minutes for the dye to be taken up

The important thing is that by both methods we have been able to get complete checks We feel that anyone who is having a very active program might use our method Anyone who does it occasionally and who likes to be able to wait after the blood has been drawn into the pipette should use Dr Randolph s method or the slight modification by Henneman, et al

for this refractoriness first, that the adrenal is fatigued, as it were which is relatively unlikely, second, a certain amount of resistance to ACTH whether it be anti hormone or some other mechanism

Dr Randolph has an excellent staining method which gives very reproducible results and allows one to count eosinophils and all the other cells, too

We adopted the method of an old German by the name of Dunger using eosin and aqueous acetone Our method in the hands of others was not always successful and the reason now has been brought out by the work of Henneman et al (Henneman Capt Philip H [M C] Hilda Wexler A B, and Mary M Westenhaver A comparison of eosin acetone and phloxine propylene glycol diluents in eosinophil counts *Jour Lab and Clin Med* 34 No 7 1017–1020 July, 1949) shown in Figs 10 and 11 When the eosinophils are shaken in our method for 2 minutes a rapid decrease in the number of eosinophils occurs In other words in this acetone mixture when 5% acetone is used the eosinophils will disintegrate rapidly if shaken hard In propylene glycol phloxine diluent eosinophils are quite stable (Fig 11)

If one follows our method closely which says that one should

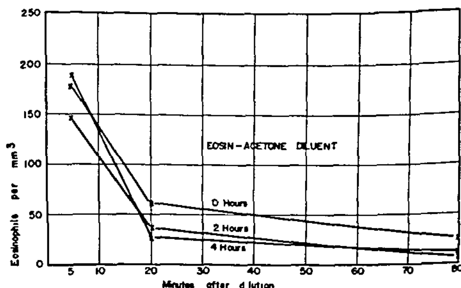


FIG 10 Circulating eosinophil counts performed at 3 time intervals showing change in counts with passage of time and aging of oxalated blood (Fig 1, Henneman Philip H Wexler Hilda and Westenhaver Mary M A comparison of eosin acetone and phloxine propylene glycol diluents in eosinophil counts *Jour Lab & Clin Med* 34 1019 July 1949)

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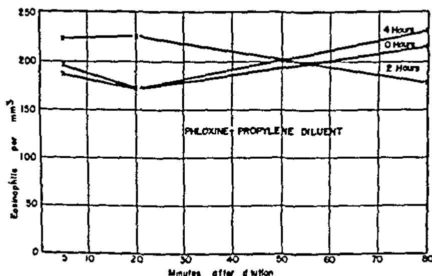


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The important thing is that by both methods we have been able to get complete checks We feel that anyone who is having a very active program might use our method Anyone who does it occasionally, and who likes to be able to wait after the blood has been drawn into the pipette, should use Dr Randolph's method or the slight modification by Henneman et al

DR WILLIAM Q WOLFSON Dr Cohn and I have been using Dr Randolph's technique for some time and have found it extremely satisfactory If one mixes the phloxine B and methylene blue diluting fluids and filters the mixture after about 48–72 hours a rather satisfactory single differential stain is obtained Some precipitation continues thereafter and we prefer to filter the stain every day or two Although it also grows somewhat weaker with time, it is quite satisfactory for at least 2 weeks Also because of the high viscosity of the propylene glycol base cleaning diluting pipettes is rather more difficult than in the case of conventional diluting fluids Hence we have preferred to by pass the diluting pipette and to use a macro diluting technique

The present procedure is as follows 3 8 ml of mixed Randolph stain are pipetted into a clean Wassermann tube and the pipette permitted to drain carefully 0 2 ml of oxalated blood are blown in and the pipette carefully rinsed 3 or 4 times with the stain The tube is corked with a clean #00 rubber stopper and permitted to stand for at least 15 minutes without agitation A shorter period tends to give less satisfactory staining but longer periods up to several hours result in improved differentiation After the tube has stood for the necessary time it is gently and repeatedly inverted for 3 minutes The counting chamber is then immediately filled from a dropper and the cells permitted to settle for 10 minutes before counting

The Randolph technique permits a rough chamber differential count We have compared a series of chamber and slide differentials in order to see whether the mononuclear count obtained from the chamber differential correlated more closely with the lymphocyte count alone or with the sum of lymphocytes and monocytes In a series of such studies the chamber mononuclear fraction was 22% the smear lymphocyte fraction 22% and the smear lymphocyte plus monocyte fraction 28% It would appear therefore that the monocytes tend to be counted with the granulocytes

In most counts there is a reasonably good correspondence between the chamber differentials and smear differentials Some difficulty arises in studies in which large doses of ACTH are given and large numbers of immature granulocytes are circulating in the peripheral blood Another precaution which must be observed in using this high viscosity stain is to take cell samples for either total white count or for differentials from both the center and peripheral portions of the counting chamber There are fairly marked differences in cell distribution in this preparation which become apparent when one uses it regularly Finally there is some suspicion that the eosinophil counts obtained by this technique after ACTH do not reflect exactly the same physiological factors as do the eosin acetone counts The latter from the studies

of Vaughan appear to be more responsive to fluctuations in cell fragility than are counts by the Randolph method I wonder if Dr Randolph would care to comment on this last point

DR THERON G RANDOLPH It should be clearly understood that in the eosin acetone technique as originally described by Dunger in 1910 and modified slightly by Dr Thorn and his associates the limiting membrane of the eosinophil ruptures within a period of 3 minutes leaving eosinophil granules adjacent to portions of the ruptured cell membrane As the granules do not stain until the membrane has ruptured it is essential that the counting chamber be charged within a period of 3 minutes in order to keep the cell fragments in close proximity As the eosinophil is one of the most fragile of the blood elements and these changes occur so rapidly I doubt if the eosin acetone hypotonic diluting fluid can be used to appraise cell fragility

2

Administration of ACTH to Normal Individuals and Patients with Intra or Extra Sellar Pituitary Tumours

H W McIntosh H T McAlpine B Singer and M M Hoffman

ROYAL VICTORIA HOSPITAL AND McGILL UNIVERSITY MONTREAL

The data to be presented were obtained in two sets of experiments The first was concerned with the administration of large doses of ACTH to normal individuals the metabolic study being conducted on a 24 hour basis The second concerned the administration of a small test dose of ACTH to patients with pituitary tumours

Five normal individuals were studied on the hospital ward They were followed for a number of days under standardised conditions The daily output of urinary chloride sodium potassium nitrogen uric acid, glucose glucocorticoids and 17 ketosteroids was determined Following this control period ACTH was given intramuscularly in divided doses every 4 hours for 24 hours until a total of 175 mgs Armour Standard had been administered In the 4 normal individuals studied at this dose level essentially similar results were obtained

Typical of the responses was that of L F a 26 year old male as shown in Fig 1 It will be seen that there was an oliguria on the day following ACTH administration This was coincident with a retention of sodium amounting to 100 milliequivalents The chlorides behaved in a similar manner There was a concomitant increase in urinary specific gravity There was a diuresis of potassium on the day ACTH was given of some 50 milliequivalents There was a retention of potassium the following day with a gradual return to normal during the subsequent days

In Fig 2, it is seen that there was a slight but definite increase in the urinary nitrogen on the day ACTH was given There was a marked increase in urinary uric acid excretion on that day and on the following day There was no change in the urinary creatinine Glycosuria occurred on the day of ACTH administration and became even more marked the subsequent day It should be noted that the

increase in the urinary nitrogen was insufficient to account for the glycosuria on the basis of gluconeogenesis and furthermore that the greatest excretion of glucose occurred at a time when the nitrogen excretion had returned to normal There was a marked increase in the urinary glucocorticoids and 17 ketosteroids

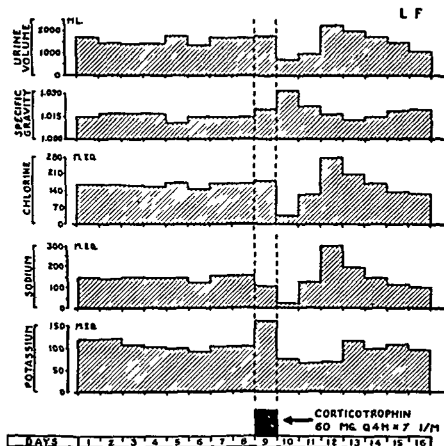


Fig 1 L F 26 year old normal male Effect of 175 mgms of ACTH (Armour Standard) given intramuscularly q 4 h for 7 doses on urinary volume specific gravity and electrolytes (Note in this and subsequent figures *the dose of corticotrophin on the chart is not given in terms of Armour Standard*)

In Figs 3 and 4 are shown the results obtained with the fifth subject H M A who received only 50 mgm ACTH (Armour Standard) over a 2 hour period There was no consistent change in urine volume specific gravity sodium chloride or potassium There is however an increase in glucocorticoids and 17 ketosteroids, although no glycosuria occurred

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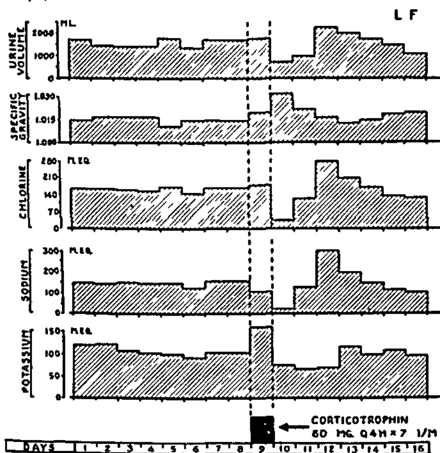


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The mechanism of the glycosuria was next investigated A normal male subject was studied under the same conditions as previously On the day prior to ACTH administration the arterial blood sugar level was determined before a standard meal and at 15 minute inter

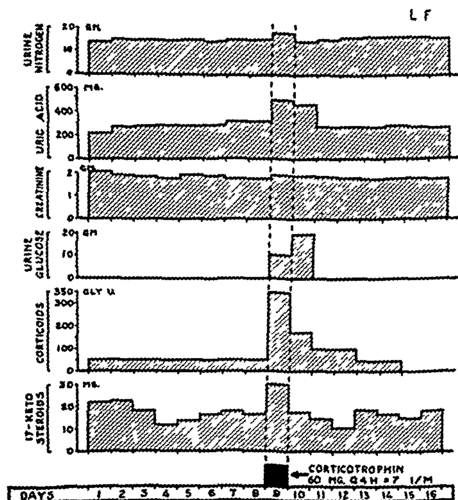


Fig 2 L F 26 year old normal male Effect of 175 mgms of ACTH (Armour Standard) given intramuscularly q 4 h for 7 doses on urinary nitrogen uric acid creatinine, glucose glucocorticoids and 17 ketosteroids

vals subsequently The results are shown in Fig 5 the curve obtained being represented by the dotted line The following day, an arterial blood sugar curve was obtained under similar conditions but the patient had received 3 doses of ACTH by that time It will be noted that a glycosuria of 2 4 gm occurred during this 3 hour period, al though the peak reached in the curve was only 5 mgm % higher than

on the control day There was, in addition, a delay in the return of the blood sugar to normal On the day subsequent to ACTH administration (Fig 6), the fasting arterial blood sugar was raised to 125 mgm % a peak value of 250 mgm % was obtained and the curve was of the 'diabetic type' A marked glycosuria of 10 4 gm occurred during this 3 hour period

These results suggest that the glycosuria following ACTH ad

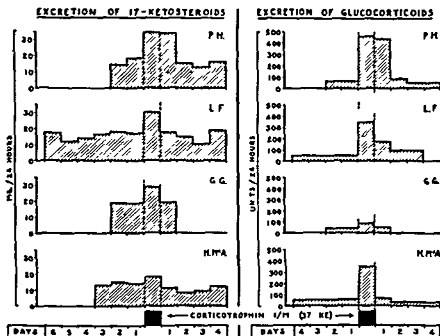


Fig 3 H McA 33 year old normal male Effect of 50 mgms of ACTH (Armour Standard) given intramuscularly in 2 doses 4 hours apart on urinary volume and electrolytes

ministration is due at first to a lowering of the renal threshold for glucose and later to a hyperglycemia

In summary then following the administration of 175 mgm ACTH to normal individuals there is an oliguria with increased urinary specific gravity retention of sodium and chloride and a potassium diuresis there is a slight negative nitrogen balance a marked increase in urinary uric acid glucocorticoids and 17 ketosteroids with the production of glycosuria due to both lowered renal threshold and hyperglycemia

The second group of experiments dealt with the administration of a small (21 mgm) test dose of ACTH The ACTH test of Thorn has

been modified, and in addition to eosinophile and uric acid changes the chloride, potassium 17 ketosteroids and neutral reducing lipids responses have been measured Urine has been collected for 6 hours following the administration of ACTH The rates of excretion of these substances are used as criteria and they are expressed as a percentage

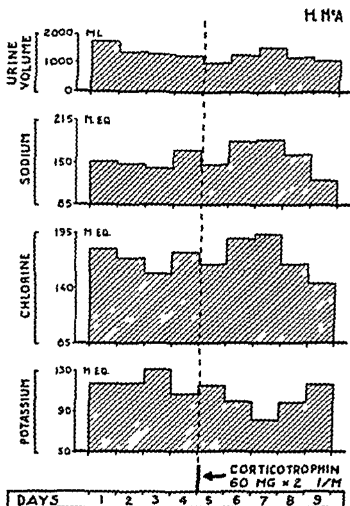


Fig 4 H McA 33 year old normal male Attention is drawn to the bottom two figures only Effect of 50 mgms of ACTH (Armour Standard) given intramuscularly in 2 doses 4 hours apart

change of their rates of excretion during an 8 hour control period prior to ACTH administration In control studies using this method significant differences were noted between the behaviour of normal individuals and patients with Addison's disease In addition to the fall in eosinophiles and rise in uric acid excretion a marked increase occurred in potassium chloride 17 ketosteroids and corticoid excretion

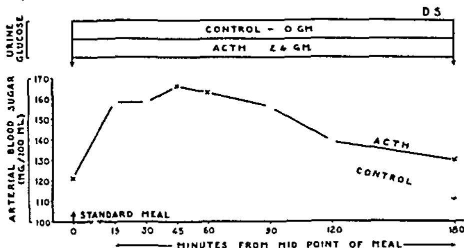


Fig 5 D S 30 year old normal male Arterial blood sugar curves following a standard meal The dotted line represents the curve obtained prior to ACTH administration The solid line represents the curve obtained after 3 doses of ACTH of 25 mgms each (Armour Standard)

D S
URINE GLUCOSE
CONTROL 0 GM
ACTH 10.4 GM
ARTERIAL BLOOD SUGAR (MG./100 ML.)
250
225
200
175
150
125
100
90
ACTH
CONTROL
STANDARD MEAL
0 15 30 45 60 90 120 180
MINUTES FROM MID POINT OF MEAL

Fig 6 D S 30 year old normal male Arterial blood sugar curves following a standard meal The dotted line represents the curve obtained prior to ACTH administration The solid line represents the curve obtained following 7 doses of ACTH given 4 hours apart a total of 175 mgms (Armour Standard)

in the normal individual following ACTH administration while patients with Addison s disease failed to show these changes

Twelve patients with pituitary tumours have been studied in this way None of these could be classed as frank cases of hypopituitarism but all showed evidence of hypofunction of the anterior pituitary lobe in one or another respect

In Fig 7 are shown the results in these cases The cross hatched areas represent the range of response in normal individuals Each dot represents the response in one patient It will be seen that there were

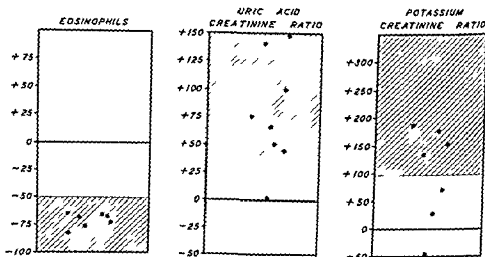


Fig 7 Result of administration of 21 mgms of ACTH (Armour Standard) to 12 patients with pituitary tumours Each dot represents the percentage change observed in the criteria noted The cross hatched area represents the range of change observed in normal controls

only 4 abnormal eosinophile responses 3 abnormal uric acid responses and 8 abnormal potassium responses In Fig 8 however it is seen that in all but one patient the 17 ketosteroid responses were abnormal and all except 2 neutral reducing lipid responses were abnormal

This suggests that the 17 ketosteroid and neutral reducing lipid responses serve as a more sensitive index of diminution in adrenal cortical function than the other indices studied It apparently required a slighter disturbance of adrenal function to result in a lessening of adrenal cortical ability to excrete 17 ketosteroids and neutral reducing lipids than is required to affect a change in the other indices especially eosinophiles and uric acid

Finally this method of study has furnished a means of discovering adrenal insufficiency preoperatively in these cases especially in sufficiency as regards electrolyte function It has thus allowed the prompt instigation of suitable preoperative and postoperative therapy in an endeavour to minimise complications due to adrenal insufficiency

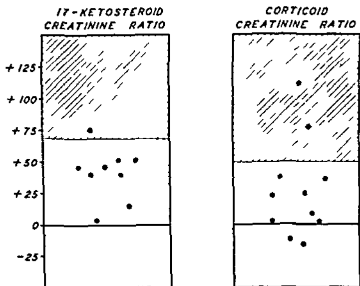


Fig 8 Result of administration of 21 mgms of ACTH (Armour Standard) to patients with pituitary tumours Each dot represents the percentage change observed in the criteria noted The cross hatched area represents the range of change noted in normal controls

DISCUSSION

DR PETER H FORSHAM I would like to make just one remark If you give 15 mg of Compound F intravenously you get a 50% fall (or thereabouts) of circulating eosinophils In other words it is a sensitive response If you give 100 mg of Compound E acetate you find less than 2 mg increase in the 17 ketosteroids in the urine of an Addisonian so you can see that 17 ketosteroid excretion is much less sensitive

It is our philosophy that the eosinophil response is the most sensitive type of response which you can get in terms of adrenocortical activation However in order to differentiate normals from pan hypo

tests there is absolutely no doubt that the use of 17 ketosteroids and corticoids are far superior to the eosinophils as shown in this paper, and we are the first to agree

However I would object to say that the test of 17 ketosteroids is more sensitive It really isn t It is much better for this kind of differentiation however

DR JEROME W CONN I would agree with Dr Forsham From our experience we need to regard the various responses as representing various thresholds so to speak of adrenocortical activity that is one point

The other point I think worth making is that even in normal individuals the responses to a given material are entirely different one from another quantitatively so that differences in quantitative responses, particularly in incomplete hypopituitarism would be difficult to interpret

DR GEORGE W THORN I think our results are in agreement with Dr McIntosh I expect he meant by increased sensitivity that the use of the 17 ketosteroids is a better way of picking up hypopituitarism Actually he has shown that a small amount of hormone would cause an eosinophil fall and the same amount of hormone is not reflected in urinary excretion

The important thing which his test shows and which our results would confirm is that in the first 4 hours (I assume this was a 4 hour test) some hypopituitary cases will respond and some won t In 48 hours you may be able to stimulate a large proportion but we have had the experience that some cases take even longer than 48 hours before you can get a good ACTH response Therefore one cannot predict

It probably has to do with the severity of the deficiency and the duration of the deficiency In our experience most of them have been able to respond after continued ACTH therapy We have often used the 48 hour test as a means of differentiating

One final point Everything Dr McIntosh says about the hypopituitary I expect is true of a patient with hypothyroidism Dr Forsham will talk about that later However, keep in mind that hypothyroidism primarily without hypopituitarism would probably give you exactly the same curve Whether any failure to respond is due to the thyroid or not in these cases we do not know

DR ROGER A LEWIS Our experience confirms that of Hoffman and McIntosh in relation to hypopituitary cases I would say the eosinophil test is the most sensitive measure of adrenal activity but the ketosteroid

excretion is the more accurate quantitative measure of adrenal activity

DR WILLIAM Q WOLFSON It is becoming apparent that complex pathways lie between the responses of the adrenal cortex to stimulation and the peripheral changes which we employ as metabolic or hematological indices of adrenal cortical response Actually it seems probable even now that reliance solely upon any single index of adrenocortical response will sooner or later result in error Later in the Conference, for example we will present observations on a patient who showed an unexplained rise in eosinophiles in response to ACTH At this time it may be of interest to note the unusual distribution of responses in a migraine patient who was studied in Boston by Dr John R Graham

The observations are summarized in Table 1

Table 1

EFFECTS OF 25 MGM OF ACTH IN A PATIENT WITH SEVERE MIGRAINE

Adrenal Cortical Index	*Change in Indices*	
	1/25/49	*9/24/49*
Blood eosinophiles	−77%	−70%
Urine urate/creatinine	19%	−26%
Urine potassium/creatinine	113%	146%

The basal values of the various indices were within normal limits The decrease in eosinophils and increase in urine potassium/creatinine ratio was normal in both trials while the change in the urine urate/creatinine ratio was markedly substandard on both trials

As Dr Forsham and Dr Thorn have pointed out changes in various indices are not always proportional because of the different shapes of the dose response curves For example they have found that 4 mg of ACTH will cause a 50% decrease in circulating eosinophiles as a solitary effect However I do not believe that one can choose a dose of ACTH which will give a rise in urine potassium/creatinine ratio of over 100% with little or no change in the urate/creatinine ratio in the urine One seems to be forced to assume either that these functions actually are under the control of different steroids or that the peripheral pathways of response are unusual in this patient The literature contains suggestions that potassium metabolism may not be entirely normal in certain patients with migraine The families of subjects with periodic paralysis for example have been found to contain an unusually high percentage of migraineurs Moreover we have ob

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3

The Effect of ACTH During the Neonatal Period

Eleanor Venning

ROYAL VICTORIA HOSPITAL AND McGILL UNIVERSITY MONTREAL

These studies were carried out at the McGill University Clinic in collaboration with Dr Charles Reid of the Department of Pediatrics The purpose of these investigations was to study adrenal response during the neonatal period

The adrenal gland of the newborn infant differs from that of the adult At birth the adrenals are relatively large structures and the cortex is composed of an outer or true cortical part and an inner part the fetal cortex This fetal cortex grows rapidly during the last trimester of fetal life and at birth begins to degenerate

Earlier studies on full term and premature infants showed that both groups excreted small amounts of biologically active corticoids at birth and that within a few weeks of life an increase in the excretion of these substances could be observed

In these present studies the criteria used for measuring response to ACTH was the excretion of corticoids and 17 ketosteroids changes in uric acid creatinine ratios and the fall in eosinophils

A chemical method that of Daughaday et al was used for the assay of corticoids This method enabled us to follow daily changes in the output of these substances before and after the administration of ACTH Only male full term infants were used in these studies

On Fig 1 is charted the daily excretion of corticoids in a series of 8 infants During the first 3 days the urinary corticoids ranged from 0 040 mg to 0 115 mg per day the average output being 0 070 mg In the second week of life the average output over a period of 4 days (eighth to eleventh day) was 0 083 mg A statistical analysis of these results indicated that the difference was only barely significant Using the biological assay a definite increase was observed by the fourth week

We then tried to determine what was the minimal effective dose of ACTH (Armour) that would stimulate the adrenal of these infants

served the onset of migraine in a subject who showed an unusually intense response to 50 mg of ACTH and its prompt and complete disappearance within 30 minutes after administration of a good sized dose of potassium chloride His spontaneous attacks however, did not respond to KCl

In the patient of Table 1 100 mg of ACTH over a period of 24 hours did not completely relieve the unusually severe prolonged headache As yet our experience with migraine has been so limited that no definite statement regarding the effects of ACTH appears warranted

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and we used an increased excretion of corticoids as a measure of response The dose is expressed in terms of mg of the Armour Standard LA 1 A Beginning with 0 3 mg we gradually increased the dose to

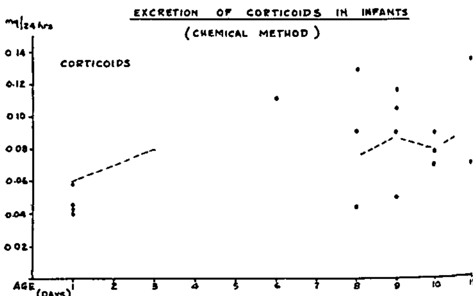


Fig 1

Fig 2

20 mg In one infant 5 mg ACTH appeared to give a definite response However 14 mg and 20 mg (in divided doses) caused a significant increase in corticoids These amounts of ACTH were all administered in the second week of life

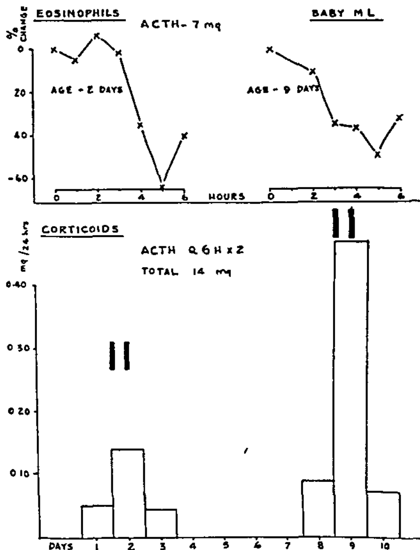


FIG 3

There is a higher mortality rate in infants during the first few days of life and it has been suggested that the adrenal might not be capable of responding adequately to stress at this time We therefore attempted to determine if there was a difference in response to ACTH in the first and second week of life In the first experiment 14 mg ACTH were

administered (in 2 divided doses of 7 mg) to an infant on the second day of life and again on the ninth day The excretion of corticoids is shown in Fig 3 At 2 days there was a small increase in urinary cor

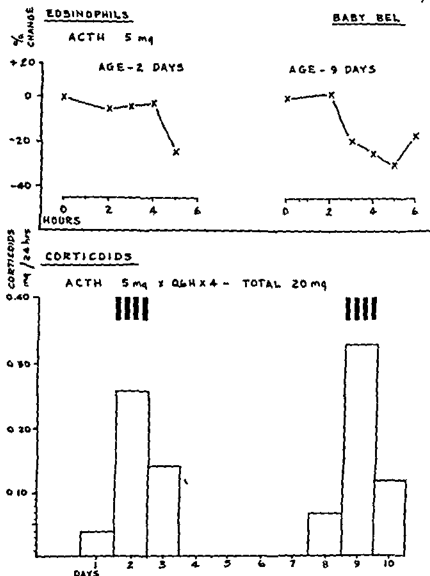


Fig 4

ticoids from 0 050 to 0 130 mg At 9 days the increase was from 0 091 to 0 468 a much more marked response

The eosinophils were followed during the first 6 hours after the first dose of ACTH i e 7 mg There was a fall in eosinophils in both instances but there appeared to be a lag in response at 2 days of life

This experiment was repeated on another infant The dosage of ACTH was increased to 20 mg (5 mg q 6 h × 4) and the results are shown in Fig 4 The difference in response was not so marked with the higher dosage The eosinophils show a slower response on the second day than on the ninth day

In this experiment (Fig 5) ACTH was given to an infant every second day during the first 10 days of life beginning with a dosage of

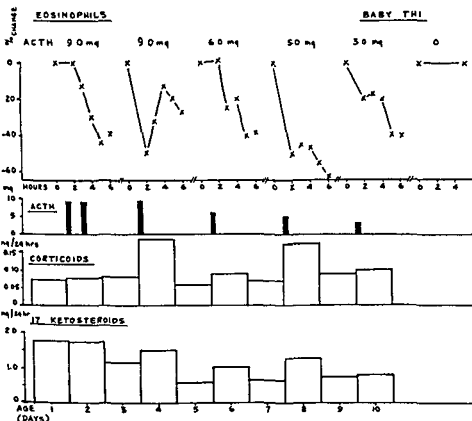


Fig 5

18 mg and gradually reducing it to 3.0 mg which is below the minimum effective dose

At 2 days of age following the administration of 18 mg ACTH there was no response in the output of corticoids or of 17 ketosteroids On the fourth day of life with half the amount of ACTH (9 mg) a significant increase in corticoids and 17 ketosteroids was observed As the dosage was reduced to 6 mg on the sixth day of life there was less of a response Two days later after 5 mg ACTH a significant response was again obtained With 3 mg on the tenth day no response

in steroid excretion was observed although there was a fall in eosinophils These results might be interpreted on the basis of an increased sensitivity of the adrenal to ACTH stimulation with advancing age of the infant or possibly that repeated administrations of ACTH influence the response of the adrenal

The daily output of 17 ketosteroids was somewhat higher during the first 3 days of life and in spite of repeated injections of ACTH gradually fell to lower levels

It is difficult to evaluate the response of the eosinophils to ACTH in this infant At all dose levels of ACTH there was a fall in eosinophils and there did not appear to be any quantitative relationship between dosage and rate of fall

URIC ACID AND CREATININE RATIOS

In all these experiments uric acid creatinine ratios were measured but the results were so variable in these infants that no significance could be attached to them

In conclusion, ACTH (Armour) when administered to infants will cause an increase in the excretion of corticoids and 17 ketosteroids and a fall in eosinophils The minimum effective dosage is in the order of 5 to 7 mg Preliminary studies indicate that the adrenal of the 2 day old infant is less responsive to ACTH than that of the 9 day old infant

DISCUSSION

DR ROBERT KLEIN We have done work that confirms Dr Venning s findings However we use much smaller doses of ACTH which enables us to get a little sharper break

Using 1 mg as the initial dose up to roughly the first 4 or 5 days of life we rarely found a significant fall in eosinophils However using the same small dose at 7 days or thereabouts, in the same patients we *found a very adequate fall of eosinophils at the end of 4 hours*

Using 1 mg 4 times a day in a few cases we have found the same increases in the responsiveness of the ketosteroids and the neutral reducing lipids but from this very small series there is evidence that the salt retention effect does not take place or is not as responsible as soon as the other adrenal hormones

A number of infants were tested only after a week These reacted as well as did the infants who had already been tested in the first two days when they were tested after a week This would seem to rule out the possibility that the first dose of ACTH acted as a priming dose for the second test

VOICE I should like to ask whether either of the last two speakers would care to comment if the possibility of the changes seen in the second week over the first week were due to a priming effect on the part of ACTH given during the first week

DR ELEANOR VENNING It is possible that this might be partly due to a priming effect but our results do show, particularly in the last experiment that there is a failure of response on the second day of life

DR H W MCINTOSH Our findings were similar

4

Observations on Adrenal Cortical "Sugar-Fat-Nitrogen" Hormone ("11–17-OCS") and "17-Ketosteroid Precursor" Production by Normal and Abnormal Individuals of Various Ages with Comments on the Fact that (a) There May Be Two ACTH's and (b) The Normal Adrenal Cortex May Not Produce True Androgens*

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Without introductory comment comparative observations on the adrenal cortical status of infants children and older persons will be presented

Fig 1 sets forth measurements of the urinary 11–17 oxycorticosteroid output of normal healthy individuals of various ages Note that the results are expressed in terms of mg per square meter of body surface (m²) per day It is seen that with the possible exception of young infants the values found are within the same range for persons of all ages In very young infants the values may be slightly lower Fig 2 extends these observations to patients with various conditions Note here that different symbols are used to represent children and older persons Note also that the scale along the left hand ordinate is logarithmic The diagnoses are indicated for each vertical line The points on or near each line represent individual measurements the short cross bars give average values for each condition The figures shown along the vertical line representing the normal range are per centile distribution values It is seen that the values found in certain

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Fig 1 *Urinary output of 17 ketosteroids and of 11–17 oxycorticosteroids by normal individuals of various ages* Note that the scale for 17 ketosteroids is in milligrams while that for corticosteroids is in tenths of milligrams per square meter of body surface area per 24 hours The 17 ketosteroid values correspond to those reported by Talbot Butler et al in *Am J Dis Child* **65** 364 1943 The corticosteroid values were obtained by the copper reduction method reported by Talbot Saltzman et al in *J Biol Chem* **160** 535 1945 These data were published by Talbot in *Pediatrics* **3** 515 1949

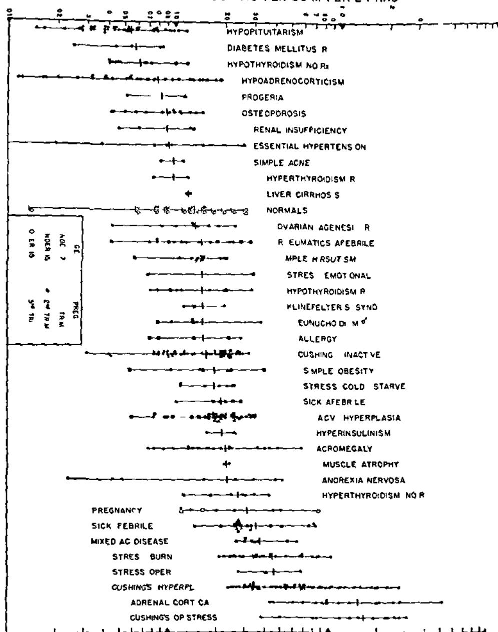


FIG 2 *Urinary 11–17 oxycorticosteroid output by normal individuals and by patients with various conditions* Note that the ordinate scale is logarithmic and that all the results are expressed as milligrams per square meter per 24 hours Note further that normal percentile distribution values are indicated along the vertical line which is located approximately in the middle of the left hand portion of the diagram One hundred % of the normal values fall be

conditions deviate from the normal and that children occupy positions similar to those obtained for adults These data coupled with those of Fig 1, suggest that insofar as 11–17 OCS production is concerned children are quite similar to adults

By contrast, Fig 1 also shows that the 17 KS output of children is very low up to about 8 years even when the values are expressed on a per m basis After 8 years there is a marked rise in 17 KS output to adult levels This observation suggests that an important alteration in adrenal cortical function occurs at about the eighth year In fact the term 'adrenarche' has been suggested by Dr Fuller Albright as an appropriate designation for the time of onset of this change The occurrence of this change raises interesting questions concerning its causation Since we have evidence that preadolescent children are as capable as adults of excreting 17 KS in their urine when given appropriate hormonal substances (such as testosterone propionate) it seems quite unlikely that the spontaneous change in urinary 17 KS output during adolescence is due to an alteration in intermediary metabolism of adrenal steroids Two other possible explanations for this phenomenon come to mind One is that the responsiveness of the adrenal cortex to ACTH may change at the time of the adrenarche This again seems unlikely since preliminary studies have shown that Armour ACTH prompts 17 ketosteroiduria in preadolescent children as it does in adolescents and adults This suggests that normal preadolescent children would be excreting appreciable amounts of 17 KS if their pituitaries were producing similar adrenocorticotrophins There remains the interesting possibility that the human pituitary produces two types of ACTH one concerned with adrenal cortical 11–17 OCS production the other with 17 KS production If this thesis is correct it must be assumed that the former is produced throughout life and that secretion of the latter is held in abeyance until the time of the adrenarche

To return to the urinary 17 KS it has been held extensively that those adrenal cortical substances which give rise to urinary 17 KS have an androgenic nitrogen anabolic action This thesis invites certain comments First the only clinical changes seen in association with 17 ketosteroiduria in normal adolescent and adult females and in castrate males (who have no extra adrenal source of androgens)

low the top of this line none of the values fall below the bottom of the line The normal range is considered to be approximately between 90 and 10 percentile levels Each point on the other vertical lines shown in the chart represents an individual determination The symbol used indicates the approximate age of the subject The short horizontal line intersecting each vertical line representing each condition indicates the average value for patients with that condition

are pubic and axillary hair growth and acne. That is, these types of individual ordinarily fail to show any such signs of true androgenic action as clitoral hypertrophy, penile growth, deepening of the voice, etc., even though their urinary 17 KS output be at high normal levels. Such observations do not appear to be in keeping with the contention that normal urinary 17 KS precursors are androgens.

Contrariwise, it is known that children and other patients with adrenal cortical virilism do show gross evidences of adrenal cortical androgenic hormone action. As shown in Table 1, the urinary 17 KS

Table 1

QUANTITATIVE RELATIONS BETWEEN TOTAL URINARY 17 KETOSTEROID OUTPUT OF CHILDREN WITH EARLY CONGENITAL ADRENAL CORTICAL VIRILISM (DUE TO ADRENAL CORTICAL HYPERPLASIA) AND MAXIMUM NORMAL OUTPUT OF NORMAL ADULT WOMEN*

Patient No	*Sex*	*Age yrs*	*Surface area m²*	*Urinary 17 KS*		*Ratio Observed 17 KS Output to Adult Normal**	
				mgm per day	*mgm per m² per day*	*mgm basis*	*mgm per m² basis*
1	M	2.5	.6	8	13	0.6	1.4
2	F	6	1.0	14	14	1.0	1.6
3	F	2.5	0.75	9	12	0.6	1.3
4	F	5	1.0	8	8	0.6	0.9
5	M	9	1.15	8	6	0.6	0.7
Average						0.7	1.2

* The maximum 17 KS output for normal adult women is taken to be 14 mgm. per day. Assuming the average surface area of adult women to be 1.6 m², the maximum normal value on a surface area basis is 14 ÷ 1.6 = 9 mgm. per m² per day.

values found for such patients are not necessarily higher than those of non-masculinized normal adult females. This is true both when the values are considered in absolute terms (mg. per day) and in relative terms (mg. per m² per day—see right hand columns). This finding suggests that the virilism shown by these patients is not necessarily explained by a simple quantitative abnormality in adrenal cortical 17 KS precursor production. On the contrary, it suggests that the virilism may be due to the production of qualitatively abnormal adrenal cortical urinary 17 KS precursors.

A number of investigators including a number present at this meeting have demonstrated by means of extensive chromatographic separation and isolation studies that the urinary 17 KS "pattern" of adrenal cortical virilism patients differs considerably from the normal. Using a micro chromatographic technique recently evolved in our laboratories, we have found the same thing. This is shown in Fig 3. Here the numbers along the abscissa are eluate fraction numbers. The percent of the total material recovered in each fraction is indicated by the scale along the left hand ordinate. The shaded area indicates the range found for normal males plus females. The individual curves are for individual patients with adrenal cortical virilism. It is clearly evident that these patients give abnormal curves.

Such evidence suggests strongly that there are qualitative differences between the adrenal cortical urinary 17 KS precursors produced by normal individuals on the one hand and by patients with adrenal cortical virilism on the other. Those produced by the former appear to have dermatotropic properties in the sense that they induce pubic and axillary hair growth and acne but not to be androgenic. Only patients with adrenal cortical virilism produce adrenal cortical hormones which act like testosterone to prompt masculinization and nitrogen anabolism.

DISCUSSION

DR LAURANCE W KINSELL One comment in terms of secretion of known steroid compounds both of which are strong androgens.

Testosterone propionate and free testosterone are excreted from the urine as 17 ketosteroids. Methyl testosterone is not excreted at all as a 17 ketosteroid.

As Dr Talbot has brought out the urinary 17 ketosteroids are certainly only to be interpreted at the present time as indices of the production of *something* not indices of the production of some material with a specific physiologic activity.

DR J W JAILER (College of Physicians and Surgeons Columbia University New York) I guess this discussion should have been brought up after Dr Venning's paper. We have been interested in pituitary adrenal relationship in infancy but in another species namely the rat.

We have used as a stress the injection of epinephrine and as our index of adrenal response the fall in adrenal ascorbic acid (see Fig 4). We have found that if epinephrine is given to rats at 2, 4 and 6 days of age there is no fall in the adrenal ascorbic acid. At the eighth day of age we first find this fall and at 10 days we find the same. The last

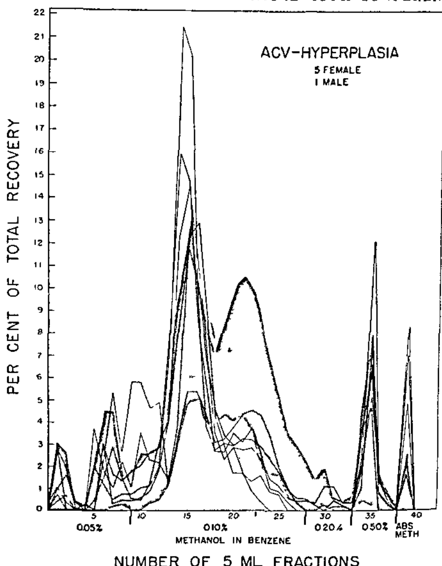


FIG 3 *Microchromatographic fractionation studies of the urinary 17 ketosteroids excreted by normal persons (shaded area) and by patients with adrenal cortical virilism due to bilateral adrenal cortical hyperplasia (individual curves)* The eluate fraction number is indicated along the abscissa The composition of the eluant is indicated in the adjacent lower area The scale along the ordinate indicates the per cent of the total 17 ketosteroid material recovered in each of the 40 fractions eluted Thus the sum of the individual points described by each curve equals 100% This fractionation was carried out with the aid of a procedure to be published by A N Zygmuntowicz and N B Talbot

column shows what Long and Sayers have shown in the adult male rats

If we change the stress and refrigerate the animals for 2½ hours at 5° C (Fig 5), we find somewhat similar results namely, that there is no fall in adrenal ascorbic acid until the sixteenth day of life With this stress the fall is only 21% This would indicate that under the conditions of our experiment the effect of cold is less of a stress than epinephrine administration

This could be explained by the fact that either the pituitary is not excreting ACTH as a result of this stress or the adrenal is not respon

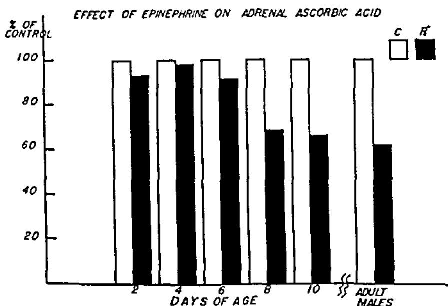


Fig 4

sive to ACTH (Fig 6) If ACTH is administered to rats at 4 days or 6 days of age a 40% fall in adrenal ascorbic acid results In other words it would appear that in the infant rat up until the eighth day of age ACTH will not be elaborated in response to stress

We have carried this a little farther and we now have preliminary evidence to show physiologically using Levin s method of deposition of fat in the liver, that at 4 and 7 days of age exposure to cold causes no increase in liver fat while at 22 days of age there is an increase in liver fat We have to work out the time relationship there

Also, as many as 3 4 day old pituitaries when injected into a 4 day old rat, do not cause a fall in the adrenal ascorbic acid This is very preliminary but it looks as if there is no ACTH as can be demonstrated by our method in a 4 day old rat I must stress that this

is in the rat which is much more of a fetus than the human newborn Its eyes are closed and its ears are closed, it cannot regulate its own temperature and has no fur

DR JEROME W CONN May I ask you what the relative absolute values of ascorbic acid are on the first day relative to the fifth or sixth?

DR J W JAILER In the rat the adrenal ascorbic acid is below 300 mgs % in the newborn, and at the twenty second day of life it is 300 mgs % Then it starts to increase to 400 at 40 days or so

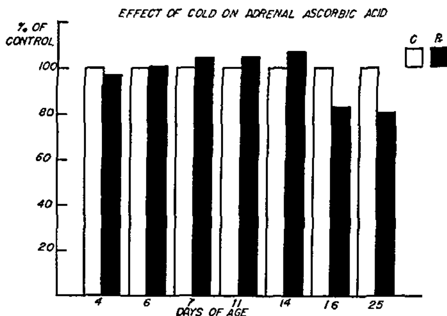


FIG 5

DR GEORGE W THORN Dr Talbot s studies are extremely important to our understanding of the nature of the response of the pituitary and adrenal cortex Two points may well be kept in mind in future discussions of this problem

1 *A patient may show a minimal response to epinephrin* suggesting adrenal cortical exhaustion but respond normally to ACTH thus suggesting either interference with the normal point of epinephrin stimulation presumably the hypothalamus or depletion of ACTH

2 The capacity of the adrenal to respond to a standard dose of ACTH does not necessarily give any indication of its actual functioning level

DR GREGORY PINCUS I would like to return to Dr Dobriner s question about ACTH and the steroid situation

I think there are a number of data which show a dissociation between 17 ketosteroid excretion and corticoid We have shown that there is a diurnal rhythm of excretion of each but that the two are not correlated with each other

I would like to call your attention to some data recorded by Dr Hechter of our laboratories He perfused adrenal glands and measured the amount of formaldehydogenic steroid and secondly the glycogenic

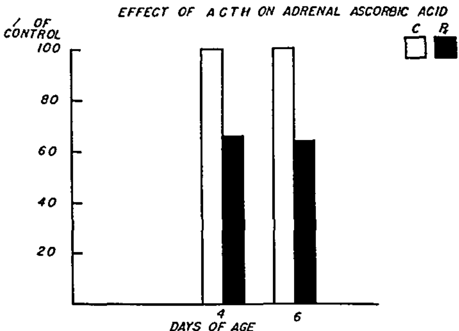


FIG 6

activity From some of his perfused glands he obtained formaldehydogenic steroid which corresponded roughly with the glycogenic activity but from other glands he obtained no glycogenic activity but considerable formaldehydogenic steroid

Therefore I say to Dr Talbot that it looks as though there is some system in the adrenal gland itself which is concerned with this differential steroid production rather than the pituitary

DR ELEANOR VENNING I would like to add one observation to Dr Jailer s remarks on the newborn infant

Apparently if the stress is great enough the newborn infant is

capable of elaborating ACTH and increasing its excretion of corticoids

We studied the excretion of glucocorticoids (bioassay) in a premature infant born of a diabetic mother (Fig 7) Within a few hours after birth severe atelectasis developed with complete collapse of one lung and partial collapse of the other The first specimen was collected during the period of stress and again after the lungs had cleared at the seventh and twelfth days The normal healthy infant excretes an average of 11 gamma glucocorticoids per day During the period of severe illness this infant excreted 54 gamma glucocorticoids per day

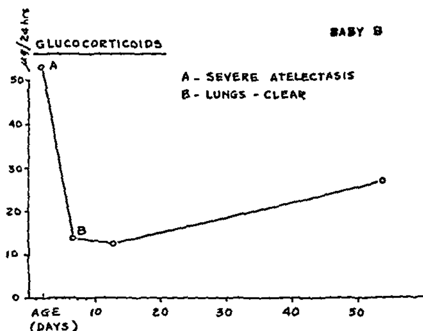


Fig 7

As the baby improved the excretion of glucocorticoids fell to normal levels

DR HENRY WILSON (Wesley Memorial Hospital Chicago) Dr Talbot is there any information on the ketosteroid response in children given ACTH after the neonatal period and before they begin to excrete ketosteroids?

DR NATHAN B TALBOT We have some preliminary information which suggests that preadolescent children and infants show proportionately as great a rise in urinary 17 ketosteroid and 11-17 oxycorticosteroid output following ACTH administration as do adolescents and adults

DR. ALBERT DORFMAN (University of Chicago, Chicago): We have data on 3 children, ages 5, 8 and 11, all of whom show a marked response to ACTH, with increased 17-ketosteroids going up to values of 3 to 5 times the control levels.

DR. J. W. JAILER: May I add another word to this? We have just given ACTH to a 3-year-old boy who had adrenal hyperplasia, whose initial 17-ketosteroids was 17 mgs. or so per day. He also was excreting 70 gamma per day of estrogens. He was given 25 mgs. ACTH a day for 4 days. During that time he got the typical rise in 17-ketosteroids excretion, that is, they arose about 100%, and nothing happened at all to the estrogens. They remained at a steady level.

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Studies of Adrenal Cortical and Anterior Pituitary Function in Elderly Men

David H Solomon and Nathan W Shock

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The degenerative phenomena of aging have frequently been linked in hypothesis to alterations in function of the anterior pituitary and the adrenal cortex However it is a sobering paradox that both hypofunction and hyperfunction of the pituitary adrenal system may be indicted with approximately equal theoretical justifications, and indeed both extremes have been cited in the literature[1 2] as explanations for the syndrome of aging In the investigations to be presented certain aspects of these hypotheses have been tested

In the first phase of the study adrenal cortical responsiveness in elderly males was evaluated by means of the ACTH test of Thorn et al [3] using 18 milligrams instead of 25 milligrams of ACTH as the single intramuscular dose This reduction in dosage was accidentally made for us by the properties of a particular lot of ACTH but it proved fortunate in that it served to widen the distribution of normal responses a highly desirable factor in a physiological study This is of course the exact opposite of what one seeks to do in using the Thorn test for the diagnosis of true adrenal insufficiency where a narrow distribution of normal responses is ideal The indices of adrenal cortical response which we studied were chamber eosinophile counts absolute neutrophile and lymphocyte counts and urinary uric acid/creatinine and potassium/creatinine ratios The subjects were all normal males, except that in the aged group many patients were accepted with diagnoses of benign prostatic hypertrophy generalized arteriosclerosis and coronary artery disease No persons with diastolic hypertension or congestive heart failure were included

Fig 1 shows the average curves of eosinophile decline in the 11 young men and the 14 elderly men in whom counts were done hourly after ACTH administration It should be noted that the initial eo

sinophile counts, the rates of fall and the eventual minima were essentially identical in the two age groups

Fig 2 describes the average responses to ACTH of the full groups of 27 young men (aged 20 through 44) and 26 elderly men (aged 61 through 89) The average 4 hour percentage decline in eosinophiles was 55% in both age groups We should mention that actually the entire frequency distributions of the eosinophile responses of the young and the old were superimposable so that if any arbitrary standard were selected essentially the same number in each age group would

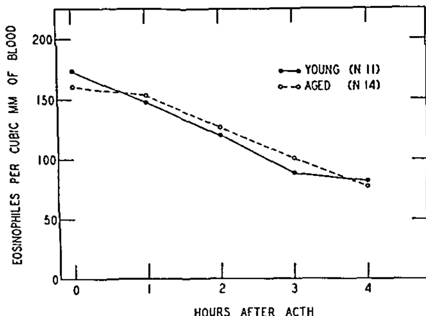


Fig 1 Mean curves of eosinophile changes after ACTH administration in young and aged men

lie below it Fig 2 also shows that the fall in lymphocytes was slightly greater in the old than in the young but not significantly so

On the other hand significantly poorer responses on the part of the elderly men were found in their blood neutrophile and urinary excretion responses The relevant evidence cannot all be presented at this time but it is felt by the authors that these last age differences represent end organ failures and that they are not inconsistent with the conclusion derived from the eosinophile data that the ability of the adrenal cortex to secrete S hormone under stimulation is unaltered by age

In the second phase of the study 0 4 of a milligram of epinephrine

was administered intravenously in saline to 15 young men and 13 elderly men The object was to evaluate the capacity of the aged anterior pituitary to secrete ACTH under stimulation *an evaluation* made possible by prior knowledge of the responses to be expected from a known dose of ACTH

The results after epinephrine are in striking contrast to those after ACTH Although the curves of percentage eosinophile decline shown in Fig 3, are parallel in the two age groups the maximum fall in the

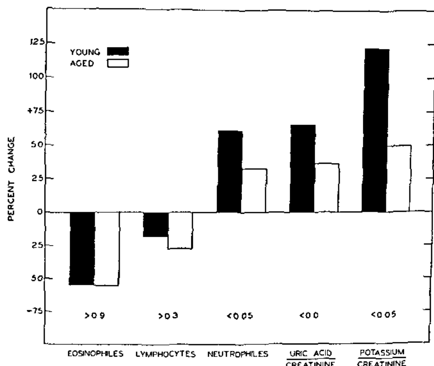


FIG 2 Average responses of 27 young and 26 aged men to ACTH administration P values are given for the difference between the age groups for each index of response

elderly was much less than that in the young When one examines the *mean maximum percentage fall in eosinophiles there is a marked age* difference (Fig 4) In the young group eosinophiles fell an average of 63%, while in the old men the average fall was 48%—a difference which would occur by chance *less than 1% of the time If one ar*bitrarily defines a fall of 50% as the minimum normal response level, only 2 of the 15 young men responded less than this whereas 7 out of the 13 old men had subnormal responses The remaining data of Fig 4 show that although small mean differences do exist there is no significant separation between the old and the young

groups on the basis of their lymphocyte neutrophile, or uric acid responses

Among the experimental groups already mentioned, there were 12 young and 13 old men who received epinephrine and ACTH on consecutive days These afforded a controlled comparison of pituitary responsiveness against a baseline of the eosinopenia produced in the same individual after a known dose of ACTH Analysis of these data confirmed the previous results Two thirds of the young subjects

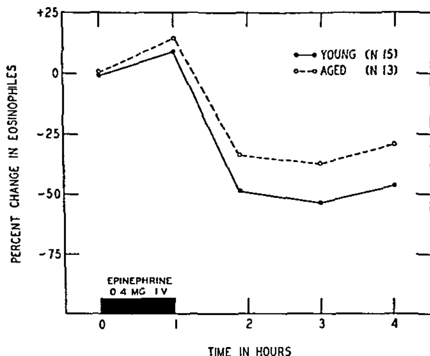


FIG 3 Mean curves of percentage eosinophile changes after epinephrine infusion in young and aged men

showed a greater response after 0 4 of a milligram of epinephrine than *they did after 18 milligrams of ACTH whereas two thirds of the aged* men showed the reverse Defining the individual s response as his maximum percentage eosinophile decline and subtracting this response figure for ACTH from that for epinephrine an average difference of +9 response units was obtained for the young and −5 units for the aged Expressing this difference as a percent of the average ACTH response the young group showed a 17% greater response to epinephrine than to ACTH, while the aged group averaged 9% *lower* for epinephrine than for ACTH Because of the consistency of these findings this difference between the two age groups in their

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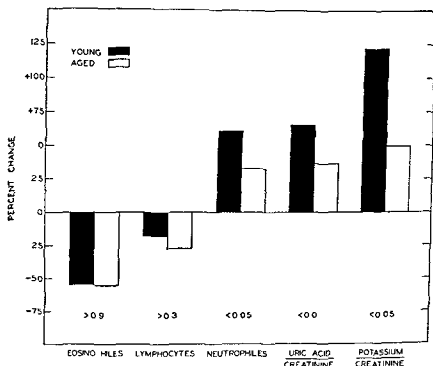


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3 Thorn, G W, Forsham, P H, Prunty F T G, and Hills A G A test for adrenal cortical insufficiency *J Amer Med Ass*, 137 1005 July 17 1948

DISCUSSION

DR FRANK H TYLER (Salt Lake General Hospital and University of Utah Medical School, Salt Lake City) One point which I think should be made is that there are other things which affect the eosinophils, lymphocytes and polys beside adrenal cortical steroids One has been pointed out here

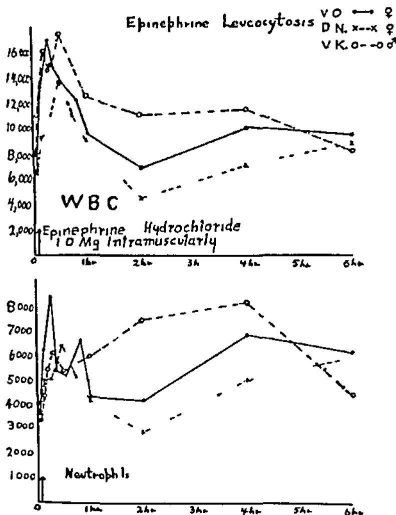


Fig 5

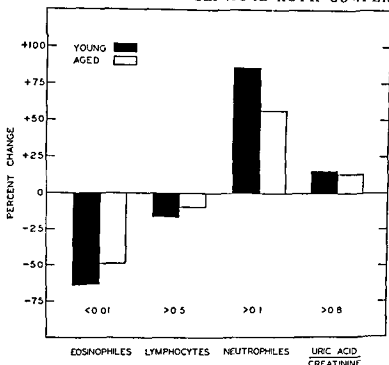


FIG 4 Average responses of 15 young and 13 aged men to epinephrine infusion P values are given for the difference between the age groups for each index of response

comparative responses to ACTH and to epinephrine was statistically significant

Conclusions

The results suggest a decreased ACTH output by the aging anterior pituitary in response to epinephrine stimulation At the same time the finding of equal responses to exogenous ACTH by old and young certainly implies that the long term output of ACTH by the anterior pituitary is unimpaired with age At least it is sufficient in the aged to maintain the functional integrity of the adrenal cortex

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different dosage levels of ACTH which confirm the dissociation between the uric acid indices and the eosinophil fall These two groups of diseases I should like to have Dr Bonner comment on with a slide

DR GREGORY PINCUS In view of the fact that we have published some papers on the excretion of 17 ketosteroids and reducing lipids in persons of various ages I should like to point out that there is a decrease in 17 ketosteroid excretion in elderly people but we have found no significant change in men up to 98 years of age in the reducing lipid output

Furthermore we have been doing 25 mg ACTH (Armour) studies in aged persons and I must say our results are quite opposite to those just reported Maybe 25 mgs represent some sort of threshold We got a much greater responsiveness in elderly people than in the young people

In every index measured including uric acid potassium sodium 17 ketosteroid and reducing lipid output and eosinophile and lymphocyte decline the elderly men in our series were as responsive as younger men This is of course only a 4 hour test and it may be that the responsivity of the aged men would flag over a longer period of stimulation

Finally as a possible commentary on our sample we used as our elderly healthy men retired policemen retired firemen and retired farmers It may be that in this group we have a sociological basis for adrenal differences

DR JEROME W CONN Dr Pincus did you compare the adrenalin response with the ACTH response?

DR GREGORY PINCUS No We used not only ACTH but the series of stress tests that we have described previously namely, the glucose tolerance test, the operation of a pursuit meter and the psychological frustration test In every one of these tests we obtained youthful responses in the elderly men

By doing the first counts at 1 hour the peak of the initial response which comes in about 15 minutes has been missed Dr A J Samuels of the University of Utah has demonstrated that eosinophiles as well as lymphocytes and polys increase by 50 to 300% during that period after the administration of epinephrine (Figs 5 and 6) Similarly,

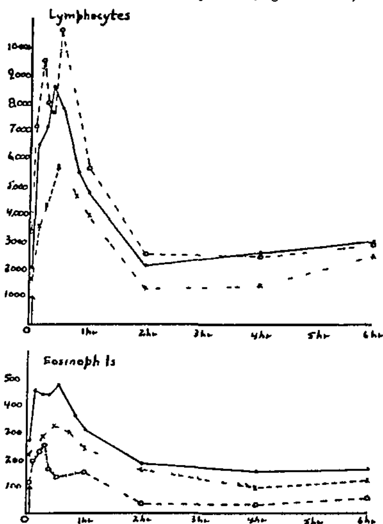


Fig 6

thyroid hormone and other substances may have independent effects upon cell counts which are not related to the adrenal mechanism as such

DR F HOMBURGER We have some data on the geriatric population with chronic debilitating disease, and also patients with cancer at

At the 80 mg dosage level there was a tendency towards a fall in blood uric acid levels in 15 out of 19 patients with and without cancer

The blood sugar level increased in 37 tests of patients with and without cancer and decreased in 2 cases with hypernephroma and 1 case each of lymphosarcoma Paget s disease of the bone generalised arteriosclerosis and progressive muscular atrophy Two diabetics with

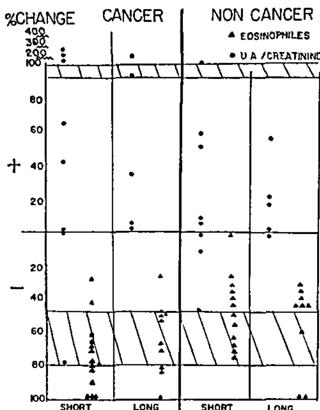


FIG 1 Changes of circulating eosinophils and of urinary uric acid/creatinine ratios following ACTH

cancer showed maximal responses whereas 2 diabetics without cancer responded like non diabetics The glucuronidase activity of the blood serum varied considerably in both directions in the cancer patients while it remained nearer constant levels in the patients without cancer

The non protein nitrogen and total protein studies revealed no changes in either group after short or prolonged stimulation

The sedimentation rate varied in all groups in all directions without any specific pattern of behavior

It may be concluded that the adrenal responsiveness of patients

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Adrenal Cortical Responsiveness in Patients with Cancer and Patients with Chronic Non-neoplastic Disease Application of the Eosinophile Uric Acid-Creatinine Response Test (ACTH) to Geriatric Patients with Chronic Diseases*

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Observations were made on the blood eosinophile count urinary uric acid creatinine excretion ratio blood glucuronidase activity blood sugar sedimentation rate blood uric acid sodium potassium *and blood proteins in 14 patients with various malignant tumors and* in 12 patients of similar ages with chronic non malignant disease These tests were done prior to and following the injection of 25 mg of adrenocorticotrophic pituitary hormone (ACTH Armour H4007 and H5409) These tests were repeated on 20 patients before and after *the injection of 10 mg of ACTH every 6 hours for 48 hours* (a total of 80 mg)

The fall of circulating eosinophiles in response to 25 mg of ACTH was within the normal range in 12 of 14 cancer patients, and in 6 of 12 patients without cancer The eosinophile response to 80 mg of ACTH was normal in 10 of 11 patients with cancer, and in 1 out of 9 without cancer Only 1 patient without cancer failed to show any change in the number of circulating eosinophiles (Fig 1)

The uric acid creatine ratio increased by approximately 100% in 3 patients with cancer at both dosage levels and in 3 patients without cancer at the lower dosage level The range of the uric acid creatinine changes in the remaining patients was from zero to 80% in all groups

* This study was aided by an Institutional Grant of the A C S by grants from the National Institutes of Health National Cancer Institute and by the Damon Runyon Cancer Research Fund

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The Levels of Circulating Eosinophils and Their Response to ACTH in Surgery Their Use as an Index of Adrenal Cortical Function*

M Roche A G Hills and George W Thorn

PETER BENT BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

Adrenal steroids of the 11–17 oxy type have been shown to produce a marked fall in the level of circulating eosinophils as measured by a direct counting technique A similar fall takes place after the injection of ACTH following the release of 11–17 oxy steroids by the individual s own adrenals The administration of epinephrine also leads to an eosinopenia which is thought to be due to stimulation of the pituitary adrenal mechanism

Simple clinical tests of pituitary and adrenal reserve have been devised on the basis of the above findings In the *ACTH test* 25 mg of ACTH are injected intramuscularly and the eosinophils are counted before and 4 hours after the injection The normal eosinophil levels vary widely between 80 and 500 eosinophils per cu mm of blood In the presence of normal adrenal cortical reserve the eosinophil level falls from 50 to 80% in 4 hours They fail to do so when adrenal cortical insufficiency is present In the Epinephrine Test 0 3 mg of epinephrine (0 3 cc of 1/1 000 solution) are injected subcutaneously and the eosinophils are counted as for the ACTH test A fall in the eosinophil levels of more than 50% is believed to indicate normal pituitary adrenal reserve

In major surgery the adrenal hormones of the 11–17 oxy type are of vital importance in the reaction of the organism against stress Hence the importance of any clinical indicator revealing the presence of these hormones in adequate amounts The present study deals with the change in eosinophil levels during and after major operations and

* Part of this work was carried out with the aid of a grant from the United States Public Health Service wh ch s gratefully acknowledged

with cancer as measured by the response to ACTH (Armour) described herein is not different from that of patients with other chronic diseases and that an increase in the stimulating dose of ACTH does not change the findings obtained with 25 mg There is in both groups an eosinophile response like that observed in normal healthy subjects and an increase of the uric acid creatinine ratio which is often less than in the normal subject

The only changes observed which may be ascribed to the presence of cancer were a more marked elevation of the blood sugar in cancerous diabetics than in non cancerous diabetics, and a greater lability of blood glucuronidase levels in the patient having various types of cancer

DISCUSSION

Covered by preceding paper

of the first significant post operative eosinophil rise Fig 4 illustrates a characteristic response to ACTH In this case, there was a marked rise in the eosinophils on the third post operative day, and at this time a near normal response to ACTH was obtained In a series of 12 patients tested at a similar period the eosinophils fell normally without exception This suggests that the adrenal had returned to a state of normal functional reserve With epinephrine however not all the patients respond normally at the time of the post operative eosino

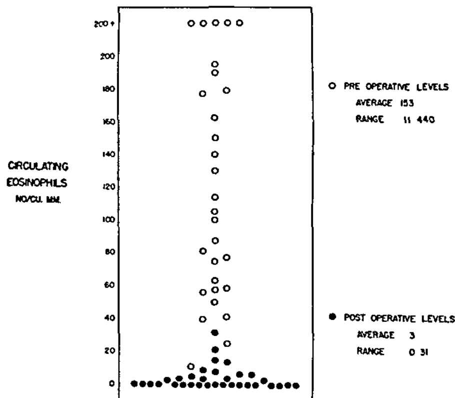


Fig 2 Levels of circulating eosinophils before and after major surgical procedures (pentothal ether anesthesia)

philia Five of the 13 patients tested showed a subnormal response An ACTH test done on these patients on the same or the following day was normal These findings suggest that there is in these patients adequate cortical reserve in the presence of a depleted or refractory anterior pituitary ACTH mechanism

PRACTICAL APPLICATIONS

From these studies one might draw several practical conclusions, each of which will be illustrated briefly by a clinical case

with the clinical evaluation of these observations when combined with the ACTH and Epinephrine tests

CHANGES IN CIRCULATING EOSINOPHILS IN MAJOR SURGERY

Eosinophil Levels During Operation

Fig 1 illustrates a typical response of the eosinophil levels during operation There is an early rise followed by a fall which is maximal 4 to 5 hours after the onset of operation

Eosinophil Levels Immediately After Operation

In all patients studied (50), the eosinophil levels 5 to 8 hours after the onset of operation was extremely low (less than 20 per cu mm)

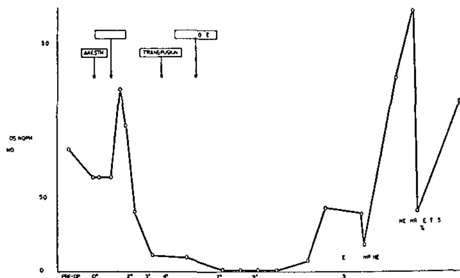


Fig 1 G T —sub total gastrectomy

In all the cases in which a pre operative value was obtained the per centage fall was found to be profound varying from 86 to 100% (Fig 2)

Eosinophil Levels During the Post operative Period

Fig 1 illustrates the further course of the eosinophil levels in one patient and Fig 3 shows the post operative eosinophil curves in 18 patients who underwent major surgery The marked post operative eosinopenia continues for 1 or 2 days Between the second to fourth day after surgery, there is usually a sharp rise in the eosinophil levels the latter attaining or exceeding the pre operative value

In order to interpret this "third day eosinophilia ACTH and epinephrine tests were performed in a number of patients at the time

1 The finding of a very low eosinophil level (less than 20 per cu mm) in the period following a major operation (4 to 24 hours) suggests a normal pituitary adrenal response and rules out hypoadrenocorticism as a cause of any post operative complications such as shock

This was illustrated by the clinical course of O L, a 29 year old woman with a 48 hour history of severe flank pain and the radiologic finding of a renal calculus She underwent uretero lithotomy shortly after admission The blood pressure fluctuated around 100/50 mm Hg and the patient appeared increasingly weak An eosinophil count of zero reassured us as to the activity of the adrenal cortex and the patient recovered entirely although her blood pressure remained low

2 Conversely during the immediate post operative period the finding of a normal or high eosinophil count points toward the diagnosis of adrenal insufficiency

This was clearly demonstrated by F T a 55 year old man who underwent resection of a localized carcinoma of the sigmoid and developed shock during the operation The eosinophil level 16 hours after operation was found to be 460 per cu mm as compared to close to zero in 12 normal patients counted at approximately the same time after their operation The patient died on the second post operative



Fig 5

% CHANGE IN CIRCULATING EOSINOPHILS

HOURS

DAYS

OPERATION

Fig 3 Changes in circulating eosinophils following major surgery

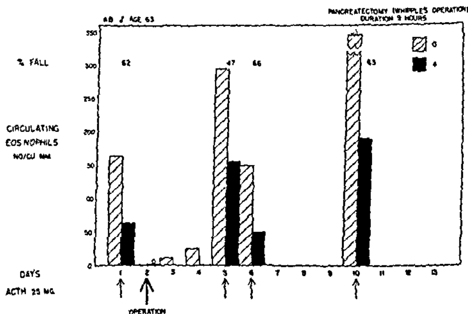


Fig 4 Pre and post operative response to ACTH

M B was a 47 year old woman with a 3 year history of amenorrhea and headaches with the actual clinical sign of bitemporal hemianopsia and with the roentgenologic finding of a much enlarged sella turcica. Pre operatively she failed to respond to either epinephrine or ACTH. An attempt was made to reactivate the adrenals by overnight administration of ACTH (25 mg every 3 hours). The eosinophils failed to respond. In spite of this operation was attempted and ether anesthesia was administered followed shortly by shock (Fig 6 left

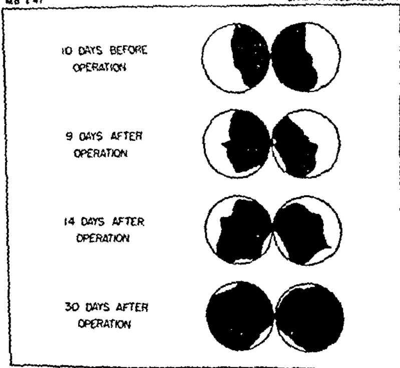


Fig 7 Changes in visual field following craniotomy

hand side) from which the patient recovered following the administration of adrenal extract and ephedrine. Operation was postponed and the patient was treated with 25 mg of ACTH every 6 hours with a resulting rise in 17 keto steroid excretion from 0 9 to 8 4 mg per 24 hours. One week later anesthesia was administered again. This time the blood pressure remained steady (Fig 6 right hand side) and a craniotomy followed by aspiration of a cystic chromophobe adenoma was performed without incident. The patient recovered full vision and health over a 1 month period (Fig 7)

5 In the post operative period if the eosinophil levels are high a

day and at autopsy bilateral adrenal tuberculosis was found—which evidently left sufficient tissue for every day existence, but not enough for the stress of operation (Fig 5)

3 A normal ACTH test pre operatively indicates that adrenal re serve is adequate and that the patient is likely to withstand ordinary operative stress, provided of course, that the pituitary is capable of stimulating the adrenal An idea of pituitary responsiveness may be obtained by the use of the epinephrine test

L S illustrates the above points She was a 37 year old woman

FIG 6 Effect of ACTH on operative course

with typical Cushing s syndrome which had been treated successfully 10 months previously with 4 500 Roentgen units to the pituitary Be cause of the presence of symptomatic leiomyomata a hysterectomy was advised The question of possible pituitary and adrenal insuffi ciencies were raised Normal responses of the eosinophils to ACTH and epinephrine pointed to a normal pituitary adrenal mechanism and the patient went through hysterectomy successfully

4 A poor pre operative response of the eosinophils to ACTH in dicates reduced adrenal function and is an indication for therapy with either ACTH if the adrenal is capable of responding to it after pro longed stimulation, or with adrenal extract in the presence of primary adrenal insufficiency

4 Recant, L Hume D M, Forsham, P H, and Thorn G W Studies on the effect of epinephrine on the pituitary adrenocortical system *J Clin Endocrinol* In press
5 Roche, M, Hills A G, and Thorn G W The level of circulating eosinophils and their response to ACTH in surgery their use as an index of adrenal cortical function *New Eng J Med*, 1949 In press
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DISCUSSION

DR FRANCIS D MOORE (Peter Bent Brigham Hospital Boston) I should like to say that the way Dr Thorn is showing us some of the important surgical aspects of this problem is very exciting wish there were more of our surgical colleagues at this meeting to hear of the work

I would like to show one slide and then make two or three additional points

Fig 8 is a balance study of an elderly surgical patient undergoing esophagectomy showing balances of nitrogen and potassium and sodium together with caloric intake Up at the top the numbers are the eosinophil counts initially showing a response to epinephrine and then a response after surgery dropping down to 5 and then coming back on the following days

You can see the loss of nitrogen and the differentially large loss of potassium and a slight tendency to load sodium which is not as dramatic in this patient as in most patients The black squares are negative balances—the cross patched areas positive The uppermost line indicates the intake

In other words surgical operation (in most patients) produces a massive ACTH like response and in thinking of treating surgical patients with ACTH we have to bear this in mind and bring it sharply into focus In a normally reactive patient a dose of ACTH at or near the time of operation constitutes only an infinitesimal addition to his own endogenous products of the hypothalamic pituitary adrenal axis ACTH given several days before surgery or in convalescence is quite another matter It must be studied objectively with particular regard to metabolic effects and the details of wound healing We are at present studying these problems

I would like also to point out that many depleted surgical patients who look clinically very ill (like the patient P J that Dr Thorn showed) in remarkable states of wound sepsis chronic depletion and

normal fall in these levels following 25 mg of ACTH indicates normal adrenal cortical reserve, whereas a poor fall indicates adrenal cortical insufficiency The results with the epinephrine test in the post operative period are governed by the state of the anterior pituitary ACTH mechanism but the results obtained appear to bear no relationship to the speed of the patient s recovery

SUMMARY AND CONCLUSIONS

Changes in the circulating level of eosinophils following major surgical operation have been presented and the possible relation of these changes to altered adrenal cortical function has been discussed

1 In the presence of normal adrenal cortical activity, there is an almost complete disappearance of circulating eosinophils during the first 24–48 hours after a major operation

2 There is usually a sharp rise of the eosinophil levels on the second and fourth post operative day associated with clinical improvement This third day eosinophilia is associated with return of normal adrenal cortical reserve

3 The finding of an eosinopenia during the first 24–48 hours after a major operation is in itself evidence of increased adrenal cortical activity

4 Conversely the finding of a normal or high eosinophil level during the first 24–48 hours after an operation suggests adrenal cortical insufficiency in the absence of allergy

5 The measurement of eosinophil fall after the injection of 25 mg of ACTH before operation is a good index of the capacity of the adrenal cortex to excrete 11 oxysteroids and furnishes a good means of pre operative prognosis

6 The response of the eosinophils to ACTH during the post operative period provides a rapid and useful means of assaying adrenal cortical reserve whereas the epinephrin response may give equivocal results

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2 Hills, A G, Forsham P H and Finch C A Changes in circulating leukocytes induced by the administration of pituitary adrenocorticotrophic hormone (ACTH) in man, *Blood* **3** 755 1948

3 Long, C N H The conditions associated with the secretion of the adrenal cortex *Federation Proc* **6** 461 1947

DR E K MARSHALL (Johns Hopkins Hospital, Baltimore) He didn t come to post?

DR GEORGE W THORN No he recovered and the diabetes insipidus disappeared

DR JAMES J SMITH Following up Dr Thorn s observation about the necessity of priming patients with whole adrenal cortex extract to get an ACTH response we have found that while many alcoholics in acute alcoholism or delirium tremens will respond well to ACTH certain numbers of them will not respond, but will respond to aqueous extract

DR JEROME W CONN I would like to make one comment, that absence of an eosinophilic response to adrenalin immediately after withdrawal of ACTH would suggest a refractoriness in the hypothalamus rather than in the pituitary gland

DR ALLAN KENYON (University of Chicago Chicago) I would like to comment on Dr Moore s slides especially with regard to nitrogen loss

I ask those who have been more closely concerned with the adrenal cortex than I whether they feel it at all possible that as far as we know now these large nitrogen losses which have been described here, and also which have been seen under other circumstances especially after fractures can possibly be due to adrenal cortex hyperactivity at that time

Whether we do not require the bringing in of some other agent if you like some other factor simply illustrates the point that we must consider whether a great many of these reactions may not be much more complex than adrenal cortex reaction as a consequence is lower

DR O H PEARSON I would like to point out that the potassium deficiency syndrome developing post operatively has been observed quite regularly after major surgery and we have fairly good evidence that it is an adrenocortical response In other words it is due to over activity of the adrenal cortex

I think it would be very hazardous to add ACTH and thus more stimulation to the adrenal cortex post operatively unless we have some evidence other than rising eosinophil counts that the patient needs more function of the adrenal cortex at this time

DR GEORGE W THORN Our own experience in the use of Compound E (Cortisone) has been of course confined to studies on patients with Addison s disease At a 100 mg dose level of Compound E in Ad

nutritional inadequacy, still will show low eosinophils, suggesting that at least to some extent their own adrenal cortices are active

One of the questions we would like to raise is whether or not further stimulation of these patients with ACTH may produce an end

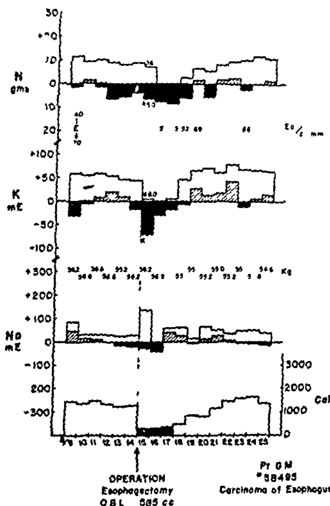


Fig 8

organ effect that is somehow or other more beneficial than that which their own adrenal cortices are doing for them

DR E K MARSHALL I would like to ask Dr Thorn what was the nature of the hypothalamic injury Could it be localized?

DR GEORGE W THORN The patient had diabetes insipidus

mechanisms than the adrenal cortex being responsible for the negative nitrogen balance that follows operation or injury

If one controls caloric intake prior to operation, and then performs either hernia or gall bladder repair, with the same constant level of caloric intake administered through the operative day and thereafter as was given in the control period one does not find a significant increase in negative nitrogen balance resulting from the surgical procedure

DR FRANCIS D MOORE How about potassium Dr Werner?

DR SIDNEY WERNER The potassium figures were in line with what you said

DR FRANCIS D MOORE There is a little differential between the two then?

DR SIDNEY WERNER That is right but not enough in our studies to say that the discrepancy is necessarily significant if distinguished from the K losses resulting from failure to provide potassium in adequate amounts during parenteral feeding

DR J S L BROWNE I think there are very marked differences in different patients with regard to the degree of nitrogen loss I fully agree with Dr Moore that if you put a patient through starvation regimes, as shown years ago you will get 7 or 8 grams negative nitrogen balance In several cases however the rise after trauma runs so high that you can get negative balances of 25 30 and even 40 grams per day To raise the caloric intake under these circumstances does not seem to control it

I would agree with Dr Kenyon and again I don t want to anticipate what I am going to say later that there are distinctly other factors than the adrenal cortex factor in patients after trauma or in acute and chronic illness

DR J R ELKINTON I would like to point out that in some of the patients to whom we gave ACTH with so called collagen diseases who were on adequate intakes of potassium we found in 7 out of 8 patients that they went into a positive potassium balance if they had an adequate intake

If they had an inadequate intake they might go into a negative potassium balance

DR WALTER BAUER What do you mean by adequate ?

disonians one usually observes only 1 to 2 grams of negative nitrogen balance

The more we study this problem the more I feel that the adrenal hormone response to ACTH is often tremendously in excess of 100 to 200 mgs

In answer to Dr Kenyon s question, it is quite probable that the larger losses of nitrogen following large doses of ACTH are due to the *action of quantities of 11–17 oxysteroids greatly in excess of 100–200* mgs of E

DR FRANCIS D MOORE We thought these were large nitrogen losses that we were seeing after surgery

Most patients lose about 7 grams a day negative balance with excretion rates in the 78–15 gram ranges A year ago we thought those were big negative nitrogen losses However when we studied patients without trauma who were purely starved and lowered the caloric intake (which is so characteristic after surgery), and compared them with Benedict s starving man we found much to our surprise that those absolute rates of nitrogen flux are not much more than one would predict on the basis of short term starvation

However that is not true of the potassium There is a definitely differential loss of K, and the K N ratio after trauma is much higher than it is after starvation

We should also point out that a small group of surgical patients (less than 15% of post operative situations) show negative balances up to 18–21 grams a day with proportionally high excretion rates This is an entirely different category of response than that usually observed and should be studied further as an abnormal adaptive response to injury

DR JEROME W CONN It is not necessary to evoke the following chain of events (adrenalin liberation → hypothalamic stimulation → ACTH liberation from anterior pituitary → adrenal cortical steroid release) to account for the increased nitrogen loss which follows trauma Ingle has shown that an increased nitrogen loss after trauma occurs in force fed bilaterally adrenalectomized rats maintained on a constant dose of cortical steroids In other words the extra loss of nitrogen following an alarming stimulus will occur in the absence of increased cortical steroid secretion and it is not necessary to implicate the pituitary adrenal cortical system to account for all the phenomena observed after trauma

DR SIDNEY WERNER (College of Physicians and Surgeons New York) I should like to agree with Dr Moore and Dr Kenyon about other

level is markedly reduced, and when the drug is stopped levels higher than those noted before the onset of therapy are observed

That the secondary high levels of eosinophiles are thus presumably due to the cessation of corticoid secretion by the adrenal rather than the increased excretion of nitrogen retaining steroids (Browne et al) is further borne out by the inability of parenterally administered testosterone to affect the circulating eosinophiles

DR JEROME W CONN It is difficult to reconcile our present concept of the alarm reaction with the facts that have been pointed out and with the fact that a patient with Addison s disease fails to go into negative nitrogen balance with ACTH in large doses

DR J R ELKINTON If they were getting 50 or more milliequivalents per day

DR FRANCIS D MOORE Is that a single dose of ACTH or what?

DR J R ELKINTON That was in doses from 4 to 8 days of 25 to 200 mgs per day

DR GEORGE W THORN Dr Conn in considering changes in potassium balance three points should be kept in mind First when a patient is stimulated via endogenous or exogenous epinephrin, he may have increased potassium excretion as potassium becomes immediately available following glycogenolysis With Compound E he will have an initial transient loss of potassium in the urine, which is a renal phenomenon Later on continued Compound E therapy as the glycogen reserves are built up in the body he may revert to a positive potassium balance

DR HENRY WILSON Dr Engel showed that rats adrenalectomized maintained on a constant daily dose of adrenocortical extract, and injured had a perfectly normal increased output of urinary nitrogen with a concomitant increase in potassium The adrenal cortex is not necessary for this response

If one has a patient being subjected to chronic injury such as lupus erythematosus and if that inflammatory process is immediately stopped when ACTH or Compound E is given of course the patient will tend to go into positive nitrogen and positive potassium balance, which may or may not outweigh the negative nitrogen and potassium balance which is a direct metabolic effect of the hormone

Whether or not we get a positive or negative will depend on whether the inflammatory process in the beginning would impair the metabolic effects of the stearates

DR J L GABRILOVE (Mount Sinai Hospital New York) We have studied the level of the circulating eosinophiles following simple trauma as exemplified by surgery and coronary occlusion Following a simple surgical procedure the eosinophile level falls markedly within 4 hours The marked reduction in circulating eosinophiles remains for 2–3 days postoperatively and then is followed by levels above those noted preoperatively (4–11 days) The eosinophile count then returns to the preoperative level Infection results in prolonged reduction of the eosinophile count

Similar findings have been noted following coronary occlusion

When ACTH is administered for long periods the eosinophile

100 mg of the peptide mixture daily in doses of 25 mg every 4 hours administered intramuscularly

After 5 days of peptide administration all medication was discontinued for a period of 16 days The patient then received 100 mg of whole adrenocorticotrophic hormone (This material was prepared by Dr Li also) Both Li preparations (after being dissolved) were placed in a boiling water bath for 10 minutes

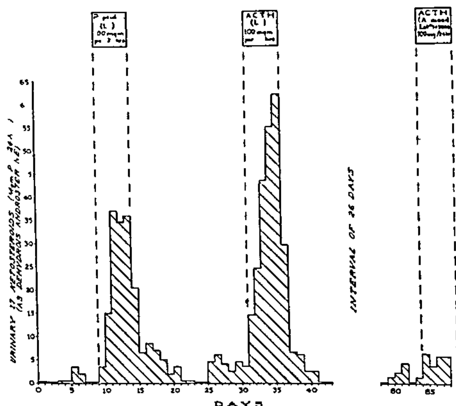


FIG 1 17 Ketosteroid excretion in response to the administration of different adrenocorticotrophins

After a lapse of more than a month he received whole adrenocorticotrophic hormone (Armour Lot #H 3806) The metabolic effect of these various materials is shown in the figures which appear on the following pages

In Fig 1 are shown the 17 ketosteroid values It is apparent that this man had a baseline 17 ketosteroid excretion which averaged approximately 2 mg /24 hours During the period of peptide administration, there was a very striking increase in the 17 ketosteroid excretion up to a maximal figure of 36 mg /24 hours Return to the base

8

Metabolic Effects of a Peptide Mixture Derived from ACTH (Li) in Comparison with Those Resulting from Whole ACTH Administration in a Human Subject*

Laurance W Kinsell C H Li Sheldon Margen † George D Michaels and Robert N Hedges‡

with the tech cal a stance of Lila E S ter Carl T A d rson a d Ma e E H tch n

METABOLIC RESEARCH UNIT UNIVERSITY OF CALIFORNIA–U S NAVAL HOSPITAL OAKLAND AND THE DIVISION OF MEDICINE UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL SAN FRANCISCO

In 1948 Li reported that a peptide mixture prepared by hydrolyzing whole adrenocorticotrophic hormone retained its ability to stimulate the adrenal cortices in hypophysectomized rats [1] In March 1949 he further reported some of the physical characteristics of this peptide mixture Prior to his departure for Europe in August 1949 he placed in our hands 500 mg of this peptide mixture All protein material had been removed by precipitation with 10% trichloracetic acid and the average size of the peptides present in the residual material was estimated to be 7 to 8 amino acids

Patient HAL a 60 year old male with classical rheumatoid arthritis was selected to receive this material ** He was placed upon a chemically constant food intake for a period of many days prior to the administration of the peptide When his nitrogen excretion had been relatively constant for a period of more than 6 days he received

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* This work is supported by grants from the Research Division of the Bureau of Medicine and Surgery U S Navy (BuMed #007046) from the Office of Naval Research under a contract between the latter and the University of California

† Schering Research Fellow in Endocrinology 1948–49 and Damon Runyon Research Fellow 1949–50

‡ Lieut (j g) MC USNR

** Drs Ephraim Engleman and Marc Krupp of the Veterans Hospital San Francisco gave helpful clinical advice in the course of this study They will be co authors of a paper describing the entire study (which is still proceeding at this time)

had 17 ketosteroid excretion values of considerably greater magnitude although at no time did he reach the levels noted on the preparations previously reported This may relate to some change of responsiveness of the patient himself or may relate to significant qualitative differences in the adrenocorticotrophin preparations

In Fig 2 is shown the method used for charting of balance studies, in the figures which will follow It will be noted that intake is charted

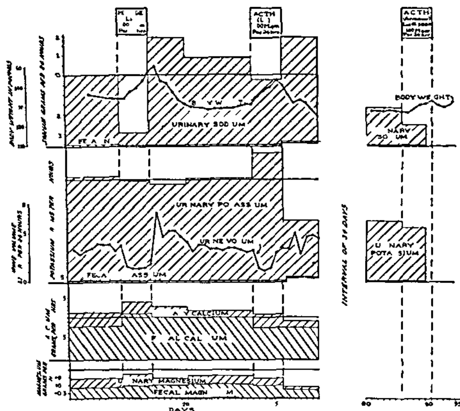


Fig 3 Sodium potassium calcium and magnes um balance data

from the heavy superior line downward Output is charted from the lower most line upward It is apparent that if the hatched area falls below the upper heavy line the individual is in positive balance whereas if the hatched area goes above the heavy line the patient is in negative balance

In Fig 3 it will be noted that there was a very marked sodium retention and a very marked decrease in urine excretion during the administration of the peptide The whole ACTH (L1) caused fluid retention of approximately the same magnitude but a very much lesser

line level was not achieved until approximately 1 week after the cessation of peptide administration During the administration of the Li preparation of whole adrenocorticotrophic hormone, a very striking increase in urinary 17 ketosteroids occurred, up to a maximal level of more than 60 mg /24 hours Again the baseline level was not reached until approximately a week after the discontinuance of hormonal ad ministration

It was found necessary to temporarily discontinue the chemically

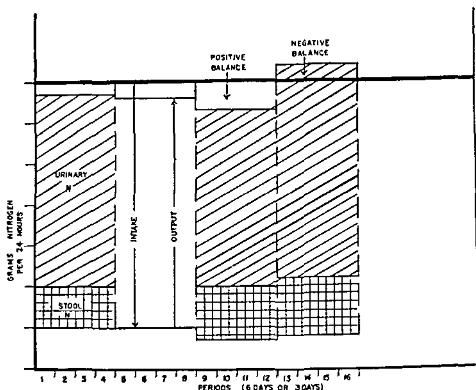


FIG 2 Schema for interpretation of balance study charts

constant diet in this patient for an interval of 26 days On its resump tion it was found that the 17 ketosteroid excretion was little changed from his original baseline level Administration of ACTH (Armour Lot H 3806) in a dosage of 100 mg daily resulted in a maximal 17 ketosteroid excretion of 6–7 mg /24 hours Unfortunately this lot of ACTH had not been used previously in any patient In other patients it has since been found to be of considerably weaker potency than one would expect on the basis of the standardization figures *This has been* confirmed for us by the Armour laboratories This same individual when at a later date he received other Armour ACTH preparations,

resulted in response to all 3 adrenocorticotrophins As in the case of calcium, a major part of the negative phosphorus balance during peptide administration was referable to increased fecal excretion of phosphorus

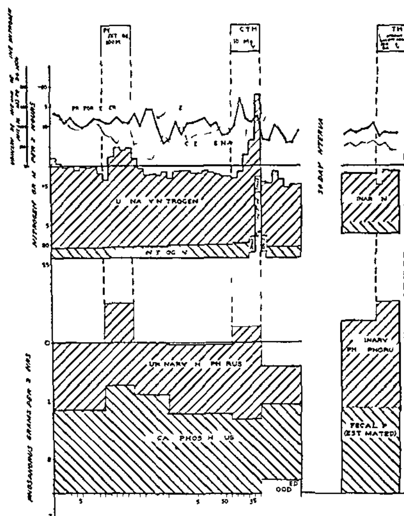


Fig 5 Nitrogen and phosphorus balance data

In Fig 5 are shown the changes in nitrogen balance and in urinary creatine and creatinine Significant increase in urinary nitrogen excretion occurred in response to the peptide mixture and to the Li preparation of adrenocorticotrophin Only slight increase in urinary nitrogen occurred in response to the Armour ACTH Significant

degree of sodium retention The Armour ACTH caused significant sodium and water retention in a fairly proportional degree Weight gain was in each instance proportional to fluid retention

The effects upon urinary potassium are difficult to interpret They may be due to qualitative differences in the adrenocorticotrophic preparations used, or they may be due to different states of responsiveness in the patient at different time intervals

Increases in calcium and magnesium excretion were most marked

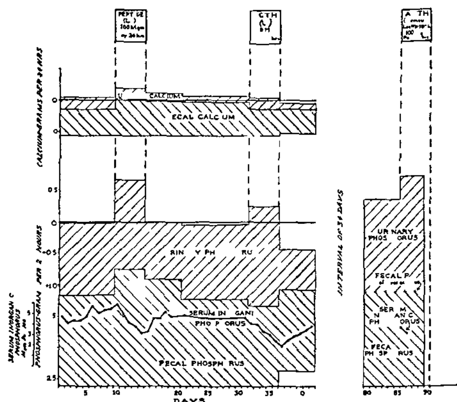


FIG 4 Calcium and phosphorus balance data

in response to the peptide administration It is of interest that a considerable portion of the calcium loss was in the feces This same observation has been noted by other members of the Conference

In Fig 4 are shown the findings in regard to calcium and phosphorus balances and in serum inorganic phosphorus during the administration of the various hormonal entities As noted above it is apparent that the peptide produced a significantly negative calcium balance and it also appears that a very markedly negative phosphorus balance resulted from the administration of all 3 adrenocorticotrophin preparations A significant fall in the serum inorganic phosphorus

level fell practically to zero in response to all 3 adrenocorticotrophin preparations It is also of interest that this individual had a rather low eosinophile count prior to the administration of any therapeutic agent and that a very striking rise in circulating eosinophiles occurred following the cessation of adrenocorticotrophin Little change was observed in hematocrit during therapy but following the first 2 treatment periods it appeared that a significant tendency toward

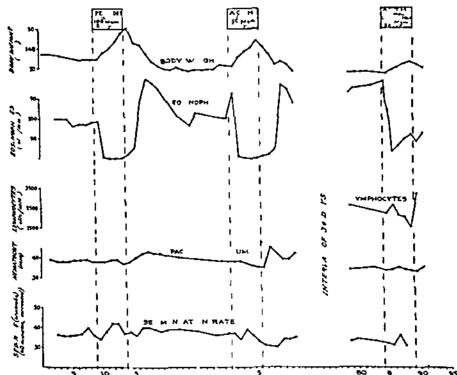


FIG 7 Body weight circulating eosinophiles and lymphocytes hematocrit and sedimentation rate values

hemoconcentration occurred This coincided with considerable diuresis in each instance

The changes in sedimentation rate were erratic during and following peptide administration but a significant fall appeared to occur during and immediately following the Li adrenocorticotrophin and the same also appeared to occur following the Armour adrenocorticotrophin The magnitude of these changes was not however of sufficient degree to deserve emphasis Very significant clinical improvement in terms of decreased joint pain and swelling and increased joint mobility occurred during the administration of all 3 adrenocor-

diminution in creatine excretion occurred during and following the administration of the peptide mixture

In Fig 6 are shown the changes in the fasting blood sugars and ketones, and in the fasting serum phosphorus serum sodium and serum potassium It is apparent that all of the adrenocorticotrophic preparations produced a rise in the fasting blood sugar levels but that a very striking increase occurred in response to the Li adrenocor ticotrophic hormone and only a slightly lesser response to the peptide

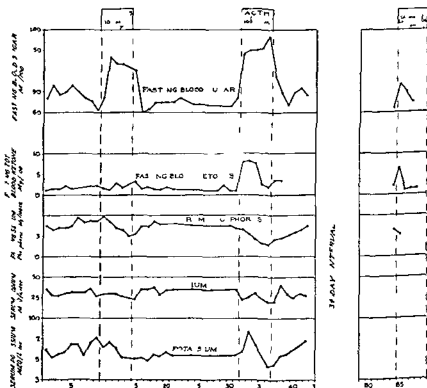


FIG 6 Blood sugar and ketone and serum phosphorus sodium and potassium values

mixture The changes in serum phosphorus may very well relate to increased phosphorylation of carbohydrate The greatest effect upon fasting blood ketones was observed when the Li whole adrenocorticotrophin was administered Such ketone elevation was transient i e, it did not continue throughout the period of administration of ACTH The changes in serum sodium and potassium are difficult to interpret and are included only for the sake of completeness

In Fig 7 are shown the changes in eosinophiles in packed cell volumes, and sedimentation rates It is of interest that the eosinophile

S³⁵ labeled methionine administered intravenously The administration of adrenocorticotrophin resulted in a very considerable increase in *labeled* inorganic sulfate, but no increase in *labeled* organic sulfur This is in contrast to the findings previously reported with testosterone[3] in which, at a time when a net retention of total sulfur occurred a

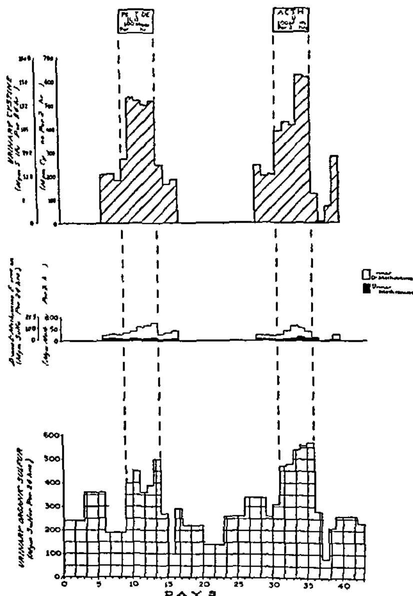


FIG 9 Organic sulfur partition (partial) in urine in response to ACTH peptide and whole ACTH

ticotrophins, and the slight temperature elevation which had been present also disappeared

In Fig 8 are shown the changes in total urinary sulfur during the first 2 studies on this patient It is apparent that a significant increase in total urinary sulfate and in urinary organic sulfur occurred during the administration of both adrenocorticotrophins and that a decrease in excretion of both of the sulfur components to values less than those

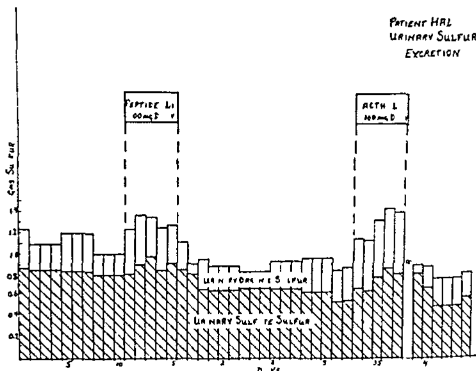


FIG 8 Urinary organic and inorganic sulfur excretion in response to ACTH peptide and whole ACTH

noted prior to therapy occurred following the cessation of the hormone administration

In Fig 9 is shown the organic sulfur partition during these same metabolic periods It is apparent that significant increases in urinary cystine and in urinary methionine occurred, but it is equally apparent that these two amino acids account for only about 50% of the total increase in urinary organic sulfur The nature of the remaining organic sulfur material is as yet unknown The method used for cystine also determines glutathione cystine Hence this tripeptide does not account for any of the as yet unidentified organic sulfur

Studies were also carried out on this patient using tracer doses of

S[35] labeled methionine administered intravenously. The administration of adrenocorticotrophin resulted in a very considerable increase in *labeled* inorganic sulfate, but no increase in *labeled* organic sulfur. This is in contrast to the findings previously reported with testosterone[3] in which at a time when a net retention of total sulfur occurred, a

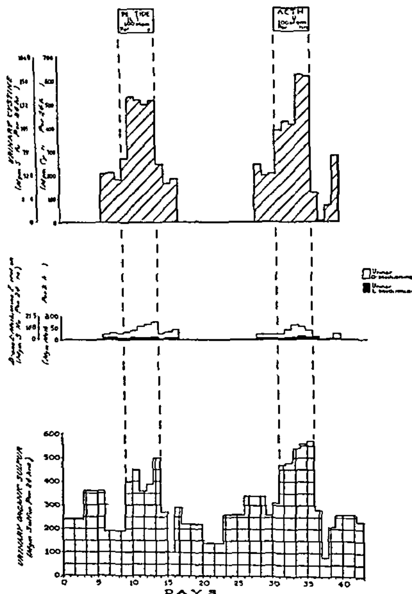


FIG 9 Organic sulfur partition (partial) in urine in response to ACTH peptide and whole ACTH

significant increase of *labeled* urinary organic sulfur was observed A portion of these data are shown in Fig 10

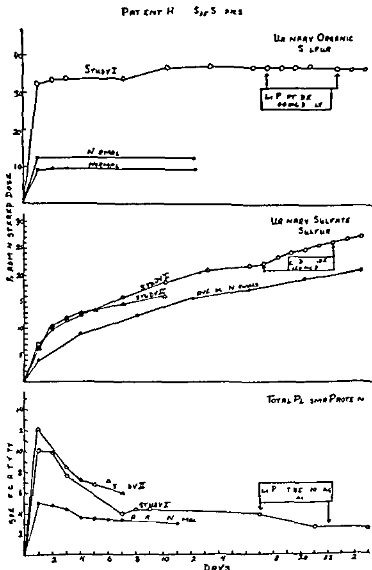


FIG 10 Response of S^{35} labeled urinary organic and inorganic sulfur and of S^{35} in plasma protein in response to ACTH peptide

DISCUSSION

Regardless of how efficient the production of adrenocorticotrophin from natural sources may become a supply which depends entirely upon such sources would be grossly inadequate in view of the in

creasing demand for this material. We have therefore been pleased to find that a mixture of relatively small peptides has great ability to stimulate the adrenal cortex and in so doing to produce a metabolic pattern comparable with that observed in the same individual in response to whole adrenocorticotrophin preparations obtained from natural sources. It is not yet known whether one or more than one peptide is responsible for the entire metabolic effect of this peptide mixture. Also, the exact size of the peptide or peptides concerned is not known. It appears probable, however, that the size of the active peptide is in a range which makes synthesis not only possible but probable. Whether such synthesis will require 6 months or many years at the present time no one can say. In view of the impressive therapeutic responses to adrenocorticotrophin which have been reported here and elsewhere, it is apparent that a program designed to produce such a synthetic material should be pursued with considerable vigor.

Many of the metabolic changes above reported are essentially identical with those noted by other members of this Conference. The labeled and unlabeled organic and inorganic sulfur data merit some comment. In brief, it appears that in an individual who had received tracer dosage of S^{35} labeled methionine 2 weeks before receiving ACTH, the following urinary pattern emerged during ACTH administration:

1. Increased total sulfate
2. Increased *labeled* sulfate
3. Increased organic sulfur (unlabeled)
4. No *labeled* organic sulfur

On the basis of previous observations, one may assume that all S^{35} has been incorporated in protoplasm well before 2 weeks after its administration. Hence the increase in labeled sulfate indicates that increased tissue catabolism occurs in response to ACTH.

The interpretation of the absence of any *labeled* organic sulfur despite the impressive increase in unlabeled organic sulfur is not so simple. It is probable that some inhibition of renal tubular reabsorption of organically bound sulfur is a necessary assumption. The lack of labeled material probably means that almost all of this organic material is derived from recent dietary sources rather than from protoplasm. The opposite picture is observed when testosterone is administered.[3]

It is also worthy of note that the initial excretion of phosphorus was considerably greater than could be accounted for on the basis of combined calcium and nitrogen excretion (that is, in terms of average calcium and phosphorus composition of bone and of nitrogen phosphorus ratios in average protein tissues). Dissolution of a large

amount of tissue with a high ratio of nucleus to cytoplasm e g lymphoid tissue, would produce such a picture

SUMMARY

A protein free peptide mixture prepared from whole adrenocorticotrophin by Dr Li has been found to have a high degree of adrenocorticotrophic activity when administered to a patient suffering from rheumatoid arthritis The metabolic changes were comparable with those resulting from the administration of whole ACTH to the same individual

BIBLIOGRAPHY

1 Li, C H Conference on Metabolic Aspects of Convalescence (Josiah Macy, Jr Foundation) 17 114 March 1948
2 Li C H Relative Size of Adrenocorticotrophically Active Peptide Fragments Federation Proceedings 8 March 1949
3 Kinsell L W, Margen S Tarver H Frantz, J McB Flanagan E K, Hutchin M E, Michaels, G D, and McCallie D P Studies in Methionine Metabolism III The Fate of Intravenously Administered S^{35}-Labeled Methionine in Normal Adult Males, in Patients with Chronic Hepatic Disease, Idiopathic Hypoproteinemia and Cushing's Syndrome Accepted for publication in the *Journal of Clinical Investigation*

DISCUSSION

DR JEROME W CONN I would like to make two comments First we have data which confirm Dr Kinsell s with respect to total sulfur balances in that ACTH causes an increased urinary excretion of both inorganic and organic sulfur which cannot be accounted for on the basis of protein catabolism alone

The other comment is that as we look over these data we are reminded again of the possibility of the existence of more than one ACTH Some of the differences in responses to the different materials may be on the basis of total ACTH present or on the basis of actual qualitative differences in the compounds

DR JOHN R MOTE I believe that everyone here has learned from experience that our labelled potency does not always correlate with clinical results particularly since the investigators have been working with disease *syndromes* It has occurred on more than one occasion that our bioassay was in error since patients who were under full con

trol with one preparation escaped when switched to another preparation It must be realized that the Sayers and Sayers bioassay technique depends upon the measurement of only one thing and there is an inherent error in this technique to the end that a statistical variation of less than plus or minus 20% is considered good

On the other hand in the human patient not only do you have the ability of observing objective changes but the investigator is able to measure a number of variables both clinical and laboratory wise in the same individual It is I believe for these reasons that it has been possible for the investigator to tell us on occasion rather categorically that our labelled potency was in error

I believe that it is entirely possible that the lot of ACTH which Doctor Kinsell used was in fact not as potent as the animal bioassay indicated and on the basis of the data presented by him I would be inclined to say that he was administering closer to 75 mgs a day rather than the apparent 100 mgs a day Furthermore the possibility must be considered that in the case of the small molecule there may have been a more rapid absorption with a maximal stimulating effect which might be well in excess of that observed in a preparation consisting of both large and small molecules In other words I am not convinced that any data has been presented to indicate that there is in fact any real difference between the several preparations used

DR PETER H FORSHAM Whole ACTH appeared to give you an initial ketosis shown on the chart apparently not given by the polypeptide Bennett showed that ACTH does give rise to ketosis in animals and when with us last year he was able to show the same thing with Compound E acetate in man

One wonders whether the absence of this ketosis with a polypeptide means that the adrenal cortex was stimulated to deposit so much glycogen in such a hurry that ketosis was effectively stopped or whether there is perhaps admixed with the larger molecule a ketogenic hormone of pituitary origin such as has been proposed on occasion?

DR LAURANCE W KINSELL Actually the increase in fasting ketones with the peptide was as great as Dr Bennett obtained with Compound E The scale is a little deceptive There was a rise of something more than 100% (which may or may not be significant) but the increase in circulating ketones in response to the whole ACTH was very marked

DR SIDNEY WERNER I just want to mention the possible importance of differences in rates of absorption with purer or with different types of ACTH preparations in influencing biological activity

amount of tissue with a high ratio of nucleus to cytoplasm e g , lymphoid tissue, would produce such a picture

SUMMARY

A protein free peptide mixture prepared from whole adrenocorticotrophin by Dr Li has been found to have a high degree of adrenocorticotrophic activity when administered to a patient suffering from rheumatoid arthritis The metabolic changes were comparable with those resulting from the administration of whole ACTH to the same individual

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weight rises despite a fall in "theoretical" weight—an indication that there is a small amount of pitressin in this ACTH (Armour lot 37 KF) (2) this effect is not seen in days 21 thru 24 or in days 31 thru 37 (3) this effect is again seen during day 48 when ACTH L1 was being given This confirms Dr Kinsell's statement that this ACTH L1, although electrophoretically pure apparently contains some pitressin

DR GEORGE W THORN This might be an appropriate time to discuss the posterior pituitary activity in ACTH preparations in regard to balance studies

Characteristically the posterior pituitary hormone has a very short period of activity as you know and therefore when one administers ACTH giving one or possibly two injections per day you would not observe much effect on water balance However since most of us are using round the clock injections of ACTH and since in most of these metabolic studies we have a patient on a constant water intake, who is not able to reduce his water intake as his body becomes better hydrated, one often observes excessive accumulation of water, which may be difficult to differentiate from the water retention secondary to sodium retention (the action of the adrenal steroids)

If you administer to a patient with diabetes insipidus with a 24 hour urine output of 8 000 ml , 0 1 unit of posterior pituitary hormone every 4 hours, you will bring his urine volume down to 4 000 ml If you give him 5 mgs of ACTH every 4 hours you can maintain the same urine volume as you do on one tenth unit of posterior pituitary antidiuretic principle Regardless of what the animal assay shows you do get a good antidiuretic effect in most of these preparations Is this all due to contaminatory posterior pituitary hormone in the ACTH *preparation or is there an inherent antidiuretic effect of* ACTH?

Again while Dr Kinsell s figures showed hemo dilution it is difficult to interpret the mechanism of the dilution because of simultaneous salt retention in that particular experiment If one could give a small dose of ACTH polypeptide to a patient with diabetes insipidus and show one did not obtain an antidiuretic effect we would have made a great step forward in the solution of this problem

DR FREDERIC C BARTTER I would like to say a little about a method of distinguishing the weight gain due to salt retention from that which is due to water retention without salt This is done by comparing the actual weight curve during an experiment with a ' theoretical weight curve based on nitrogen plus potassium plus sodium (or chloride) according to the method described by Reifenstein Albright, and *Wells* (*J C Endocrin* 5 367 1945) When water is retained with salt these two curves run parallel to each other when it is retained without salt (pitressin effect) they diverge This is illustrated in Fig Four from our paper *Article 19 A Comparison of the Effects of* ACTH in Panhypopituitarism Ovarian Agenesis and Acromegaly showing the effect of 3 courses of ACTH and one of desoxy corticosterone glucoside on the actual and theoretical weights If you compare the actual weight (solid line) with the ' theoretical weight based on N K and Na (dotted line) you see that (1) during days 19 and 20 the actual

weight rises despite a fall in 'theoretical' weight—an indication that there is a small amount of pitressin in this ACTH (Armour lot 37 KF), (2) this effect is not seen in days 21 thru 24 or in days 31 thru 37 (3) this effect is again seen during day 48 when ACTH Li was being given This confirms Dr Kinsell's statement that this ACTH Li although electrophoretically pure apparently contains some pitressin

9

Effects of ACTH on Carbohydrate Metabolism in Normal Human Beings

Jerome W Conn

UNIVERSITY HOSPITAL UNIVERSITY OF MICHIGAN ANN ARBOR

I want to make a few points first and then show quite a number of slides which I will go through rapidly

In a series of 10 prolonged balance studies upon normal young men and women given 50 to 100 mg per day of Armour Standard ACTH we have observed the following

1 Glycosuria in all varying from 2 grams to 50 grams per day

2 The initial glycosuria is due to decreased renal reabsorption of glucose

3 Hyperglycemia and diabetic glucose tolerance curves begin to appear after 24 hours of ACTH except in one subject in whom normal tolerance for carbohydrate persisted

4 The amount of glycosuria bears little relationship to the degree of negative nitrogen balance or to the time of appearance of the latter

5 A close temporal correlation exists between glycosuria and increased urinary excretion of uric acid

6 The diabetes produced is relatively insulin resistant

7 Fasting blood glutathione decreases as carbohydrate tolerance is lost and returns to normal upon cessation of ACTH with a more gradual return of normal carbohydrate tolerance

8 Administration of reduced glutathione during a course of ACTH induced diabetes produces temporary cessation of glycosuria and a fall of blood sugar

9 In clinical Cushing s Syndrome associated with diabetes and low levels of blood glutathione administration of reduced glutathione converts a diabetic glucose tolerance curve to a normal one

10 In a typical case of Cushing Syndrome exhibiting normal carbohydrate tolerance blood glutathione was found to be higher than in any normal subject so far studied

I would like to run through these slides and point out just a few things on each slide

Fig 1 shows a normal female given ACTH in this period 50 mgs per day There is negative nitrogen balance the peak at 7 gm negative nitrogen balance per day The white bars represent glycosuria This is the blood sugar and this is the uric acid excretion

Fig 2 is on the same individual showing the concomitant metabolic data The upper graph represents sweat sodium and chloride under "ACTH

There is an initial sodium and chloride retention and a potassium diuresis with ACTH By the fourth ACTH day these values have re-

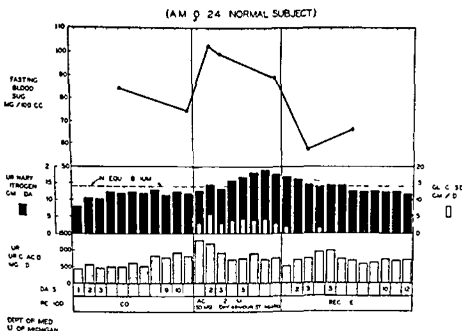


Fig 1 Effect of ACTH upon fasting blood sugar and upon urinary glucose nitrogen and uric acid

bounded to baseline values On cessation of ACTH a great diuresis of sodium and chloride and a potassium retention occurs This shows the eosinophils getting down to zero bounding back on the second day getting back to zero and staying there with some rebound when the ACTH is stopped

Fig 3 is on the same normal individual and shows the glucose tolerances 7 days after ACTH as compared with the control and the post ACTH tolerance

Fig 4 is on a normal individual of the same age given the same ACTH (another normal female) and given it on the same days as the other normal female with all of the chemistry done simultaneously

EFFECT OF ACTH UPON SWEAT Na AND Cl IN RELATION TO URINARY N CI K GLUCOSE NITROGEN URIC ACID AND EOSINOPHILS

(A M ♀ 23 NORMAL CONTROL)

Fig 2

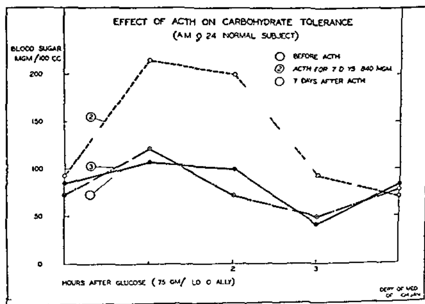


Fig 3 (From Conn Jerome W Louis Lawrence H and Wheeler Clayton E Production of temporary diabetes mellitu in man with pituitary adrenocorticotropic hormone relation to uric acid metabolism *Jour Lab and Clin Med* 33 651 June 1948)

In this normal girl with the same dose and the same batch, every thing else the same, there is no negative nitrogen balance Glycosuria occurs The re bound of glycosuria occurs on the fourth day after ACTH is stopped, associated with an increased uric acid such as you saw in the first girl and there is a relationship between the uric acid columns and the glycosuria columns

Fig 5 shows the associated metabolic data showing essentially the same responses (but less quantitatively) that we saw in the first

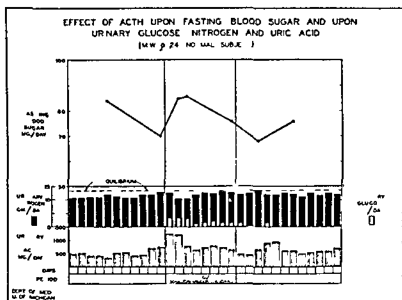


Fig 4 (From Conn J W Louis L H and Johnston M W Studies upon mechanisms involved in the induction with adrenocorticotropic hor mone of temporary diabetes mellitus in man 8 3 Proc Am Diab Asso, 1948)

subject The eosinophils increased when ACTH was stopped in this individual

Fig 6 shows the one subject who failed to give us a diabetic glucose tolerance curve although as compared with the base line flat curve this shows somewhat less tolerance but would not be regarded as ab normal carbohydrate tolerance

Fig 7 shows a very responsive man who has negative nitrogen balance in the ACTH period which amounts to as much as 9 grams per day of negative nitrogen balance He responds with a higher rise of the fasting blood sugar up to 140 and with a sustained increase in uric acid excretion

Fig 8 shows that his responses in everything are very great, and

EFFECT OF ACTH UPON SWEAT Na AND Cl IN RELATION TO URINARY Na Cl K GLUCOSE URIC ACID AND EOSINOPHILS

(M. W. ♀ 23 NORMAL SUBJECT)

Fig 5

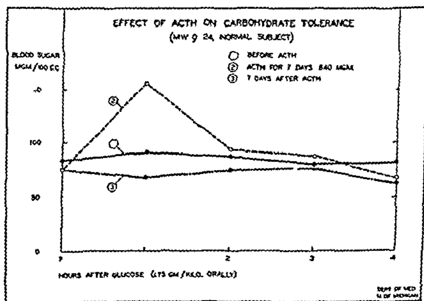


Fig 6 (From Conn Jerome W Louis Lawrence H and Wheeler, Clayton E Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone relation to uric acid metabolism, *Jour Lab and Clin Med* 33 651, June 1948)

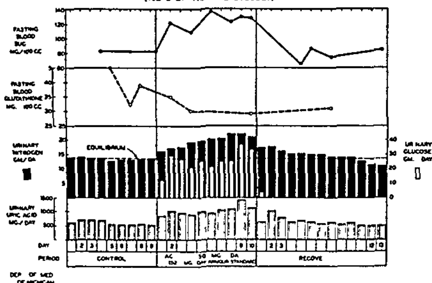


Fig 7 (From Conn J W Louis L H and Johnston M W Studies upon mechanisms involved in the induction with adrenocorticotropic hormone of temporary diabetes mellitus in man 8 3 Proc Am Diab Asso 1948)

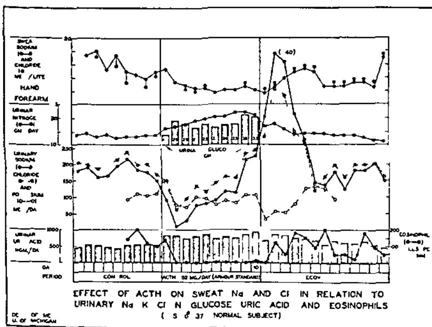


Fig 8

EFFECT OF ACTH UPON SWEAT Na AND Cl IN RELATION TO URINARY Na Cl K GLUCOSE URIC ACID AND EOSINOPHILS

(M W ♀ 23 NORMAL SUBJECT)

Fig 5

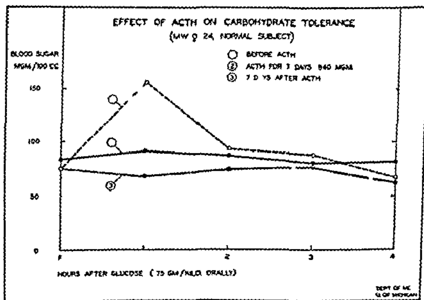


Fig 6 (From Conn Jerome W Louis Lawrence H and Wheeler Clayton E Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone relation to uric acid metabolism *Jour Lab and Clin Med*, 33 651, June 1948)

Fig 11 is interesting In the normal man whose data you just saw, the glucose tolerance test was done on the sixth ACTH day 330 units of insulin had been given over the 5 day period prior to this glucose tolerance test and it failed to prevent a diabetic glucose tolerance curve Four days after ACTH there is still a delay and then it is normal after 10 days

Fig 12 shows data from an experiment on another normal young

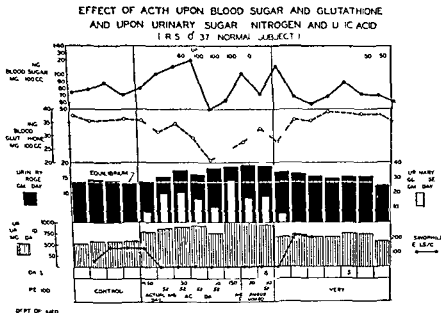


Fig 10 (From Conn Jerome W Louis Lawrence H and Johnston Margaret W Metabolism of uric acid glutathione and nitrogen and excretion of 11-oxysteroids and 17 ketosteroids during induction of diabetes in man with pituitary adrenocorticotropic hormone *Jour Lab and Clin Med* 34 255 February 1949)

man You will notice that the glutathione in the last 2 days of ACTH fell rapidly and was associated with a sharp increase of glycosuria

You all know what reduced glutathione is This is the material we have injected intravenously The SH group is what we think is important here (Fig 13)

Fig 14 shows blood sugars done hourly throughout the entire ACTH period (8 AM to 4 PM) Note that the fasting blood sugar is rising with each day of ACTH Where you see the asterisks it means glutathione was given intravenously 1 hour before You will note that the blood sugar is rising at each of the hours during the ACTH period but that there is a reversal of this trend wherever the glutathione was

you will notice the very tremendous retention of sodium and chloride —the tremendous diuresis of sodium and chloride when ACTH is stopped His electrolyte metabolism is thus markedly affected Glucose 36 gms per day is the largest amount at this time The eosinophils stayed at zero

Incidentally his initial sweat sodium and chloride values are very low We find such people to give the greatest responses to ACTH

Fig 9 shows his glucose tolerance curves After one day of ACTH

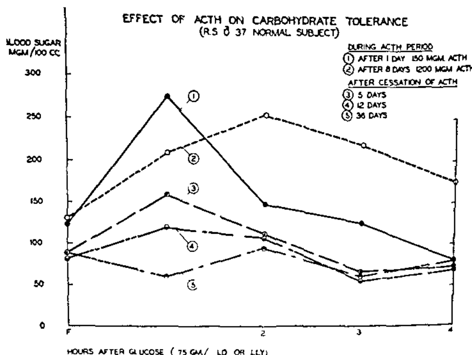


Fig 9 (From Conn Jerome W Louis Lawrence H and Wheeler Clayton E Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone relation to uric acid metabolism *Jour Lab and Clin Med* 33 651 June 1948)

he showed this diabetic curve which at the end of 2 hours was 150 After 8 days he had a very prolonged diabetic curve, the blood sugar level being 175 at the end of 4 hours

Fig 10 is a little complicated, and I can t take time to explain all the details but I put this slide in to show the relative insulin resistance This is the same individual you just saw Glycosuria persists in spite of 35, 35, 60 100 100 and 100 units of insulin a day On the fifth and sixth days of ACTH the fasting blood sugar is coming up again despite 100 units of P Z I per day

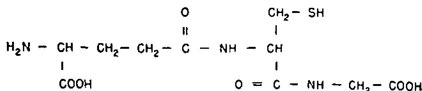
Subject D E (Normal)

Period	Days	ACTH	17 K S	Cortin	Glycosuria	Glutathione**	Uric Acid
		mg /day	mg day	mg day	gm /day	mg 100 cc	mg /day
Control	1	0	12.9	—	0	37.0	—
	2	0	12.6	0.9	0	31.2	490
	3	0	13.4	0.6	0	—	525
	4	0	10.0	0.7	0	34.3	538
	5	0	12.[illegible]	0.7	0	30.0	505
ACTH	1	26x	12.3	1.8	0	30.5	709
	2	26x	14.0	1.6	0	32.1	650
	3	26x	19.2	1.3	0	27.5	690
	4	52x	20.1	1.4	4.1	28.0	710
	5	52x	22.3	1.4	2.7	—	728
	6	52x	27.1	2.0	4.5	32.1	730
	7	52*	27.5	2.6	12.6	22.0	885
	8	52*	27.5	8.5	8.4	1[illegible].7	740
Recovery	1	0	11.3	5.1	0	32.5	510
	2	0	9.4	5.9	0	31.4	594
	3	0	10.6	1.3	0	37.2	392
	4	0	10.0	1.3	0	—	508
	5	0	13.0	0.9	0	32.5	640
	6	0	16.9	1.7	0	32.2	435
	7	0	18.9	5.1	0	—	450

* mg (Armour Standard) Lot—37 K G—More diabetogenic
x mg (Armour Standard) Lot G 59703—Less diabetogenic
** Fasting blood glutathione at end of each 24 hour period

FIG 12 Subject D E (normal)

REDUCED GLUTATHIONE
(GLUTAMYL - CYSTEINYL - GLYCINE)
($C_{10}H_{17}O_6N_3S$)



GSH

FIG 13

given It apparently had very little effect when given on the seventeenth post ACTH day

Fig 15 shows that the urinary glucose from 8 AM to 4 PM during the ACTH period was 1 gram 5 14, and then it dropped to 4 during the glutathione day and then 16 and 24 Here is the average blood sugar that day as compared with the others The glutathione was

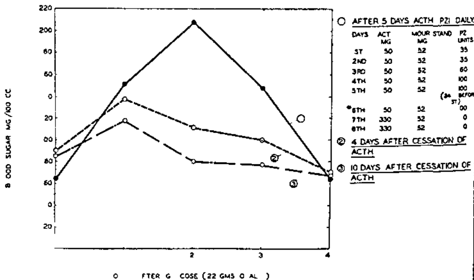


Fig 11 (From Conn Jerome W Louis Lawrence H and Johnston, Margaret W Metabolism of uric acid glutathione and nitrogen and excretion of 11 oxysteroids and 17 ketosteroids during induction of diabetes in man with pituitary adrenocorticotropic hormone *Jour Lab and Clin Med* 34 255 February 1949)

given after the fasting blood sugar had been drawn on the fourth ACTH day

Fig 16 shows the urinary glucose in relation to injections of glutathione You will recall that there were only 4 grams of glucose eliminated in the 8 hour period on the day of G S H The stippled periods represent the hours during which the injected G S H was effective Qualitatively there is no sugar in the urine at any of those hours The effect however is evanescent It disappears in an hour or

Day of ACTH	1	2	3	GSH* (4)	5	6
Fasting blood sugar (mg/100 cc)	71	73	108	124	134	148
Blood sugar—average of 9 a m 2 p m 3 p m (mg/100 cc)	115	165	184	*157*	204	193†
Urine sugar—8 a m –4 p m (gms)	1 0	5 1	14 7	*4 0*	16 2	24 3

* GSH administered at 8 a m 1 p m and 2 p m on day No 4

† Values for this average are 198 at 9 a m , 201 at 2 p m and 179 at 3 p m GSH administered once on this day at 2 p m

Fig 15

Effect of Intravenous GSH Upon Urine Glucose* During ACTH Diabetes

Urinary Glucose in Grams

<table>
<tr><th>Time</th><th colspan="8">8AM 9 10 11 12 1PM 2 3 4</th><th>8AM 4PM</th><th>4PM 8AM</th><th>Total</th></tr>
<tr><td>ACTH Day #3</td><td colspan="2">4 637
(4 8)</td><td colspan="2">3 398
(3 8)</td><td colspan="2">1 573
(1 8)</td><td colspan="2">5 070
(5 3)</td><td>14 7</td><td>8 9</td><td>23 6</td></tr>
<tr><td>ACTH Day #4 (GSH)</td><td>0
0 151</td><td colspan="4">3 487
(3 4)</td><td>0
0 80</td><td>0
0 120</td><td>Tr
0 17</td><td>4 0</td><td>20 1</td><td>24 1</td></tr>
<tr><td>ACTH Day #5</td><td colspan="2">5 009
(5 1)</td><td colspan="2">3 544
(3 8)</td><td colspan="2">2 899
(3 1)</td><td colspan="2">4 789
(5 0)</td><td>16 2</td><td>26 8</td><td>43 0</td></tr>
</table>

*Done by Somogyi procedure as modified by Nelson (J B C 153 375 1944)
Figures in ( ) are values by the Benedict Quant Procedure

Fig 16

two Quantitatively there are only a few milligrams of glucose in the urine in these periods and the volume of urine in each of these hours was at least as large as the volume in each other hour

Fig 17 shows a patient with Cushing s syndrome The No 1 intravenous glucose tolerance curve was done before a subtotal

Effect of Intravenous GSH Upon Hourly Glycemia During ACTH Diabetes

Period	Days	Blood Sugar mg / 100 cc Fasting 8 AM	9	10	11	12	1 PM	2	3	4
Baseline	3	89								
	4	86								
	5	77								
	6	79	87	69	67	76	91	110	79	79
ACTH 68 mg / day (Armour Standard)	1	71	118	74	62	89	122	106	122	87
	2	73	155	98	77	86	167	172	152	117
	3	108	178	165	113	81	151	171	202	---
	4	124	*150	181	156	97	128	*157	*164	191
	5	134	212	207	150	134	187	201	200	165
	6	148	198	209	194	150	195	201	*179	152
Recovery	1	135	193	191	193	169	142	149	128	99
	2	76	118	116	101	101	92	92	101	92
	3	71	116	99	87	77	111	91	96	88
	4	70	128	86	69		101	101	95	81
	5	84								
	6	82								81
	17	82	93	73	86		82	*78	91	85

*G S H administered one hour before

Fig 14

was 127 days after operation and we obtained a normal curve Note the spontaneous rise of blood glutathione that had occurred in this interval also that 5 days of ACTH stimulation of the cortical remnant failed to alter materially either the fasting blood glutathione or the glucose tolerance curve

In Figs 19 and 20 I show pictures of another case of Cushing s Syndrome These are simply to convince you that we are dealing with Cushing s Syndrome

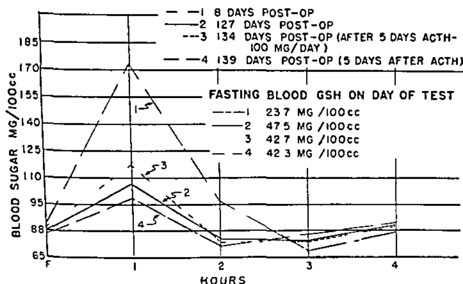


FIG 18

In Fig 20 the point is that this patient with Cushing s Syndrome gave no evidence of diabetes We were particularly interested to know why she had escaped the diabetic aspect of Cushing s Syndrome

Fig 21 is the last slide I drew it up the night before I left Ann Arbor That is why it is in my own handwriting Note that the glucose tolerances are perfectly normal one done on 8/18 and another test on 10/3 This is the curve for daily fasting blood sugar It varies between 60 and 70 The blood glutathione values which we have obtained in this patient are higher than in any of our normal subjects

adrenalectomy This patient subsequently has been cured by a 90 plus % subtotal adrenalectomy Her hypertension has disappeared the diabetes has disappeared all metabolic evidence of Cushing s syndrome has disappeared

The No 1 curve is before operation with 25 grams of glucose The

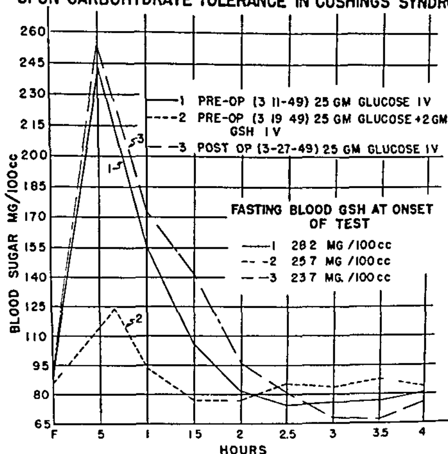


FIG 17

#2 curve is also pre operative We gave the same amount of glucose plus 2 grams of glutathione intravenously and got a normal curve Then 8 days after operation when diabetes had not yet disappeared we obtained the same curve we had obtained before operation Note that fasting blood glutathione is too low at the onset of all 3 curves

In Fig 18 the #1 curve is that obtained 8 days after operation It is still diabetic in type and the blood glutathione is still low No 2

insulin hormones They raise a number of questions that I would like to have Dr Conn answer for us

What for example, is the significance of the blood glutathione levels inasmuch as the glutathione seems to be confined largely, if not almost entirely, to the red blood cells? In other words are the red blood cell glutathione levels of themselves significant or are they significant as a reflection of what is going on in the other tissues of the body?

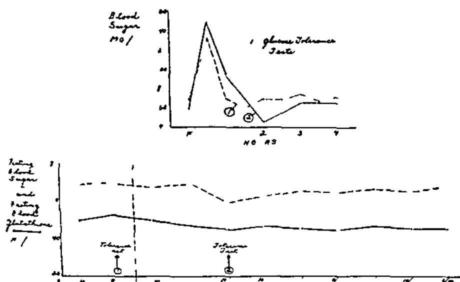


Fig 21

Secondly I should like to ask about the method for analyzing glutathione I wonder whether you used the method involving glyoxalase which I understand is the only specific glutathione method other analytical procedures only determining SH groups and assuming that they come from glutathione

Thirdly how long does reduced glutathione remain in that form in the blood stream and are metabolic effects achieved by the oxidized form as well?

DR JEROME W CONN I think the questions by Dr Shorr are very important and of course we have considered them very seriously



Fig 19



Fig 20

In the past they have been between 55 and 57 now they are running in the range of 46 to 50

DISCUSSION

DR EPHRAIM SHORR With respect to glutathione these findings are extraordinarily interesting in that they promise to give us information on a basic level about the mode of action of insulin and the counter

tion in the liver than diminished tissue utilization of glucose Later with more prolonged therapy we have observed a failure of inorganic phosphorus to fall in conjunction with high glucose curves this, we believe represents a more truly diabetic state I feel that some word of caution should be employed in terming all elevated glucose tolerance curves as being diabetic without more careful study of serum inorganic changes or respiratory quotient

VOICE If what you say about deposition of glycogen in the liver is correct then why don t you have a more definite type of sugar tolerance curve with the falling slower?

DR GEORGE W THORN I believe most body tissues are able to utilize glucose at normal or even increased rate hence the return to normal of the glucose level within the normal period and hence my caution in terming this curve diabetic with its usual implication

VOICE The point would have to be examined with some care because ordinarily you would expect some delay if you go back to the observations of some years ago

DR GEORGE W THORN Yes I agree

We have one final experiment which may be of interest If one wished to examine the glycogen content of the liver of a human subject one would be faced with the difficulty that in undergoing the operation for liver biopsy one might set in motion the endogenous ACTH adrenal mechanism and hence have a high level of glycogen in the control The thing to do is to select a patient with no anterior pituitary function

If you do a careful liver glycogen study under controlled circumstances and again following ACTH in a patient who cannot respond and you can show that his eosinophils during the control operation do not fall and that there is no evidence of any adrenal activation then you can demonstrate that *ACTH* administration markedly increases the glycogen content of his liver

DR JEROME W CONN Dr Thorn don t you think it is a question of really splitting hairs? If this situation eventually leads to the diabetic state as we recognize it then what comes before is simply a very early evidence of what happens and what we don t see in the usual diabetic patient By the time he comes to us with fully developed and persistent diabetes we should not expect to find any changes that we find on the first week of ACTH

In the first place, we don t regard the blood glutathione as meaning anything but a possible reflection of what is going on intracellularly in other tissues We also know that glutathione traverses membranes very slowly so it is possible for a sharp fall in glutathione to occur in certain other tissues without its being immediately reflected in the blood

We are quite aware that we are measuring the intracellular content of glutathione of the red blood cells We have determined the serum and it contains essentially no glutathione

Secondly methods available for determination of SH groups or glutathione are not very satisfactory We are not using the glyoxalase method because it is much too difficult for us to do for the large number of determinations needed in our work The glyoxalase method is the most specific of course

We also realize that when we measure blood glutathione by the method that we are using which is Van Potter s modification of the Benedict and Gottshalk method we are not measuring glutathione alone but we think a very large proportion of what we are measuring is glutathione

The electrometric titration of Benesh for SH groups is probably the most reliable method for determining sulfhydryl groups We are now in the process of setting up to use this method in our work

DR GEORGE W THORN There are several considerations which I should like to discuss regarding the type of diabetes produced by Dr Conn with ACTH administration in normal subjects In the beginning, we were concerned about diabetes mellitus as a possible major complication of ACTH or Cortisone therapy Practically this rarely occurs although it is obviously a danger in potential diabetics and indeed we had no difficulty several years ago in producing diabetes in patients who had experienced partial pancreatectomy

Secondly it is of interest that apparently most patients with Cushing s disease and a rather florid diabetes lose the diabetes completely with cure of the adrenal overactivity

Thirdly the Cushing s type of diabetes is known to be relatively resistant to insulin Thus, in producing diabetes with ACTH one should be on the lookout for unusual changes in carbohydrate metabolism

In studying this problem we have observed an interesting series of changes First the glucose curve is elevated as Dr Conn points out However if one checks the fall in serum inorganic phosphorus during the glucose administration it appears to be normal and not diminished as one sees in true diabetics Thus I feel that this initial hyperglycemic curve is a reflection more of increased glycogen deposi

DR GEORGE W THORN I don t want to leave any confusion in your minds We agree completely with Dr Conn I do think our differences in Stage—and I would like to get an expression generally

In our experience diabetes is not something we have had to worry about with ACTH administration over a prolonged period in a wide variety of diseases, and it would come back very normal Whereas if you talk with people who have had no experience with ACTH there are a great many other things we are much more worried about — about prolonged use of ACTH in diabetes and that fact might well be brought up at this time although it in no way invalidates the studies that have been reported

DR F L ENGEL (Duke University Durham) I would like to make a comment about some recent observations of ours which may have a bearing on the mechanism of the diabetes after ACTH namely the studies on lipogenesis from carbohydrate

We have been interested in the technique of Wertheimer, of studying the rate of glycogen accumulation in adipose tissue There is some fairly good evidence that this may quite well reflect the conversion of carbohydrate to fat

In acute experiments as you know insulin has a very striking effect in increasing the glycogen content of adipose tissue With neither adrenocorticotrophic hormone lipo-adrenal cortex aqueous extract or Cortisone have we been able to demonstrate any effect on lipogenesis from carbohydrate On the other hand and I think this has a bearing on the insulin resistance in this syndrome we have been able to show that cortical hormone (lipo-adrenal cortex or cortisone) will completely inhibit the increase in adipose tissue glycogen that occurs after insulin

DR LAURANCE W KINSELL I would like to show one slide Dr Conn which I think may have some bearing on your data and which I should like to have you comment on if you will

In the course of evaluating the peptide and the 'whole corticotrophins we have quantitated total organic sulfur methionine as such and cystine as such in the urine (See Fig 22) I might add that methionine and cystine are done by microbiological procedures The cystine method determines cystine in glutathione so the figure probably represents total urinary cystine

As you will note on the slide there is a very significant increase in total organic sulfur in methionine sulfur and in cystine sulfur in response to the adrenocorticotrophic materials One other very interesting thing is that the combined amounts of cystine sulfur and methionine sulfur account for only about half of the total increase in

DR GEORGE W THORN I agree Dr Conn except that I suspect initially we have an increased insulin production following ACTH or Cortisone therapy and I hesitate to characterize as diabetic a patient *who appears to be able to utilize glucose at a normal rate, although I* suppose in essence we are saying normal rate of glucose utilization with increased insulin secretion equals early diabetes Later with impairment in glucose utilization we all agree on the diagnosis Most of us have not had experience in the human of seeing increased glycogen deposition as the earliest stage of diabetes and this may introduce a *new concept to some although I believe it is a likely occurrence*

DR PETER H FORSHAM There is also one thing to add that it is not infrequent that in these so called Cushing s diabetics (as in your case) you can wipe out the diabetes by curing the Cushing s syndrome I think that happens a good deal more often than one sees spontaneous recovery *from the other type of diabetes*

DR JEROME W CONN I think there is a good argument in answer to that Dr Forsham If one produces diabetes with ACTH in a normal person or if one has a case of Cushing s syndrome with diabetes and finds that the diabetes disappears upon cessation of ACTH or upon adrenalectomy the situation is not at all comparable to spontaneous diabetes We realize of course that were we to give ACTH in large amounts to an individual who was born with the hereditary anlage of diabetes mellitus we might have an entirely different answer When one has a situation of ACTH diabetes in a normal person and gets a return to normal carbohydrate metabolism when the excessive cortical function stops it suggests that the resistance of the beta cells to degeneration is greater in that individual than in the individual who carries the hereditary trait of diabetes

DR PETER H FORSHAM We agree completely on that Have you ever given insulin as an insulin tolerance test with and without reduced glutathione thereby insinuating that perhaps the glutathione some*how protects insulin from destruction?*

DR JEROME W CONN Protects insulin?

DR PETER H FORSHAM Yes

DR JEROME W CONN Glutathione inactivates insulin, of course *in vitro* and I don t know of any evidence that might suggest protection of the insulin molecule by glutathione—no I haven t done that experiment

DR EPHRAIM SHORR Wouldn t that be expected from the fact that most proteins contain cystine and if you have an increased breakdown you are bound to get specific amino acids if you look for them?

DR JEROME W CONN Dr Shorr the amount of sulfur in the urine can not be accounted for by protein breakdown in the usual proportions of nitrogen to sulfur It is much in excess of that

DR LAURANCE W KINSELL I think it can be accounted for by the amino acids Those data did not include any inorganic sulfate at all it was all organic sulfate

VOICE You can point out that the sulfate excretion did not go up as much as the inorganic sulfur If you plot this data in n s ratio you will find that the n s ratio under some ACTH therapy actually goes down, whereas the other is cut down terrifically Most of the changes are accounted for on the basis of inorganic sulfur too

DR EDGAR GORDON (University of Wisconsin Medical School, Madison) In regard to Dr Conn s interest in the electrometric titration method for blood SH groups we have been using this method for about 8 months and have found it to be very satisfactory It is the technique described by Benesh and gives absolute values very much lower than those obtained by Dr Conn using the technique of Dr Van Potter We have also observed similar changes of SH titer varying with adrenal cortical activity These changes are in the same direction but of smaller magnitude than those reported here in response to ACTH stimulation

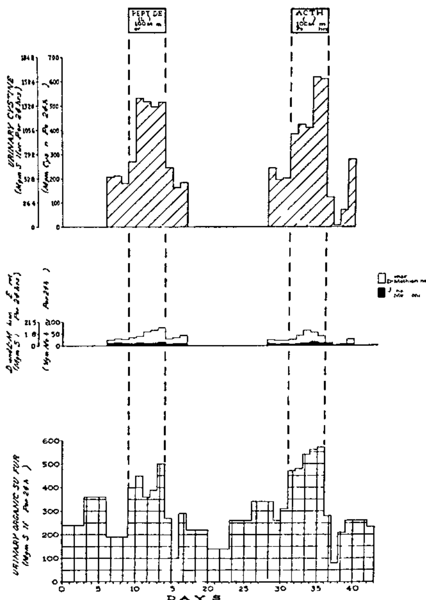


Fig 22

organic sulfur We are puzzled as to what that other half represents

DR JEROME W CONN I am not prepared to answer that question, Dr Kinsell except to say that we are not using the microbiological method, but are using the Sullivan procedure for urinary cystine With ACTH in normals we have obtained similar data to yours namely, a pouring out of cystine in the urine In addition, another increment of non cystine sulfur is excreted in excess

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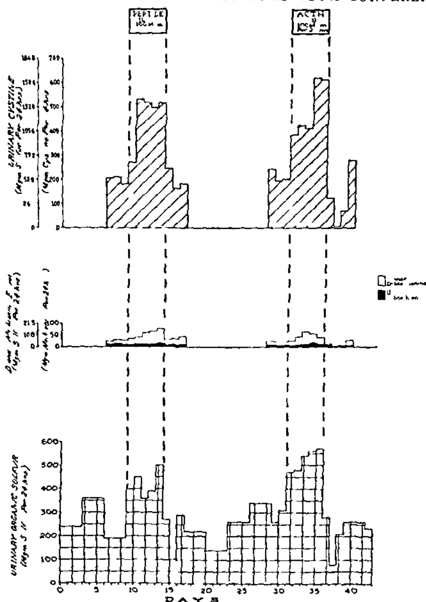


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You will note that the gluco corticoid excretion falls then rises again and remains high for about 25 days

The urinary nitrogen excretion as you see is high initially and then decreases steadily on a constant nitrogen intake and more or less

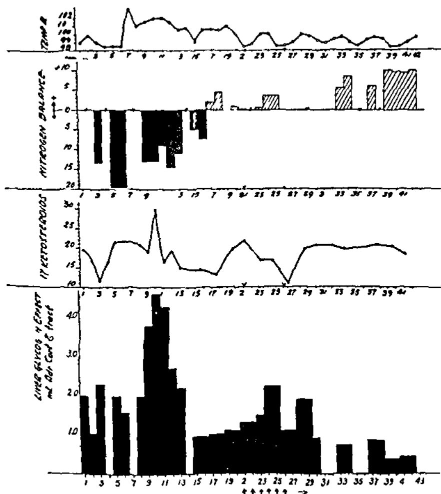


Fig 1 Case No 92 (T.s.) Male 36 burns W Ch = Wheel Chair U W = Up Walking

parallels in this instance the decline in the gluco corticoid excretion

In Fig 3 are the data relative to another fracture case In this instance the urinary excretion values range from 200 to 300 glycogenic units per day and you will note that the increased excretion continues for approximately 20 days

In Fig 4 are the data concerning a case of a laparotomy and

10

Protein Metabolism in Acute and Chronic Disease and the Relation of Protein Metabolism to the Excretion of Gluco-Corticoids

Dr. J S L Browne Louis G Johnson Victor Schenker and Eleanor H Venning

ROYAL VICTORIA HOSPITAL AND McGILL UNIVERSITY MONTREAL

There are a variety of methods of measuring adrenocorticoid function There was a period during which the rise of nitrogen excretion post operatively and post traumatically was directly associated with the excretion of corticoids We know from Dr Thorn s and Dr Conn s data as well as those of other investigators that there is a rise of nitrogen excretion when you inject ACTH into normal individuals but the rise is less than many of the extremely high values we find after trauma or after a severe burn

In Fig 1 a case of burns the values for urinary gluco corticoids rise to about 400 glycogenic units per day and stay at an abnormally high level for approximately a month The intriguing problem is the variability in the length of time that the adrenal cortex continues its increased secretion after injury or stress This is well illustrated in the data which Dr Thorn presented, namely the rising eosinophile count and the duration of the adrenal response post operatively, which will probably vary over a wide range In the above instance the adrenal on the basis of increased gluco corticoid excretion (and this is only one type of evidence) continues to over function for a period of a month It would be of interest to compare the level of eosinophiles with the level of gluco and chemical corticoids after operation to see whether the rising eosinophiles would always be accompanied by a falling gluco corticoid excretion

In Fig 2 are the data of a case of a fracture and in this instance the values rise to 200 glycogenic units per day which is comparable to the level seen after about 120 mg ACTH in normal human beings

In Fig 6 the usual urinary excretion pattern after severe trauma in a previously well nourished healthy person is shown There is a rise in urinary nitrogen I would like to say that I prefer the level of

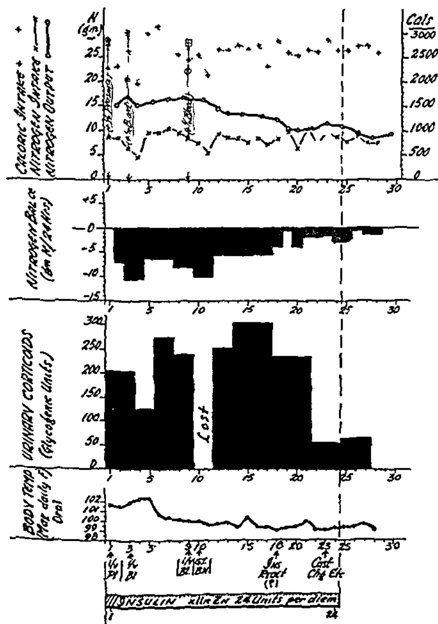


FIG 3 Case No 157 (G Wil) Male 44 fracture (femur tibia) insulin 24 days

gastrectomy It may be seen that the urinary excretion values rise to about 300 glycogenic units per day and it may be noted that the values stay up at about the 200 glycogenic units per day level for a period of about ten days

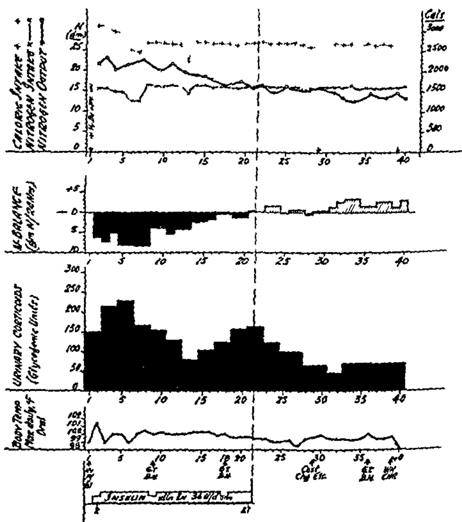


Fig 2 Case No 170 (Chog) Male 29 fracture (femur tibia) insulin 20 days

The data in Fig 5 relate to a case of carcinoma with operation in which the corticoid excretion values stay up for only 2 days We have seen other operations such as hernia and so on, in which the values remain up for only a very short period of time In this case the urinary nitrogen excretion does not rise very much

In Fig 6 the usual urinary excretion pattern after severe trauma in a previously well nourished healthy person is shown There is a rise in urinary nitrogen I would like to say that I prefer the level of

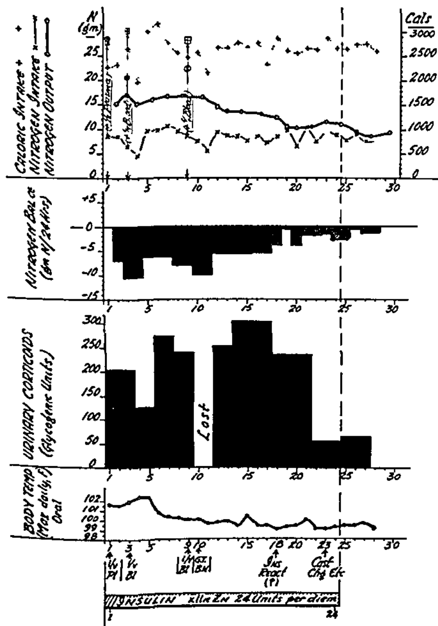


Fig 3 Case No 157 (G Wil) Male 44 fracture (femur tibia) insulin 24 days

nitrogen intake and output to be expressed rather than a statement simply of nitrogen balance. An individual can be in positive balance on 48 grams of nitrogen intake or on 10 or 6 grams of nitrogen intake. The balance alone does not adequately reflect the state of the protein metabolism.

In Fig. 7 are the data of an individual 3 months after a fractured

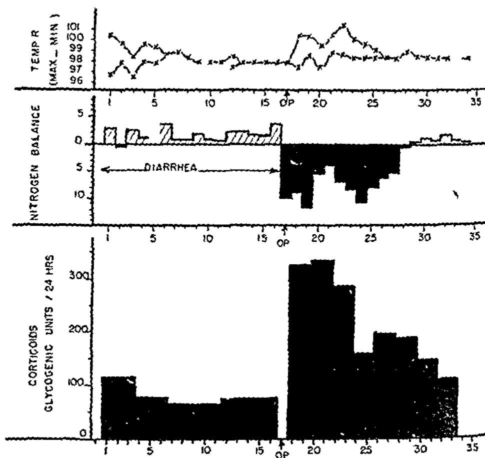


FIG 4 Case No 114 (Sh) Male 48 operation = Op

jaw and fractured femur with wound infection and a temperature of 101° F. The urinary corticoids are within what we call normal limits. That raises a point. When we say the urinary corticoids are normal we may be in error because while they may be at the same level as they are in a normal person they may reflect an adrenal secretion inadequate for the metabolic status of this individual who is chronically ill.

You will observe that in this instance, on an intake of only 800

calories and 6 grams of nitrogen with a temperature of 101° F this individual is in 2 grams positive nitrogen balance and when her intake was raised to 17 grams of nitrogen she is in something like 10 grams positive nitrogen balance which continues over a very long period of time Thus there is a difference in the status of the nitrogen metabolism in this chronically ill person and were she operated upon there would most likely be no rise after the operation

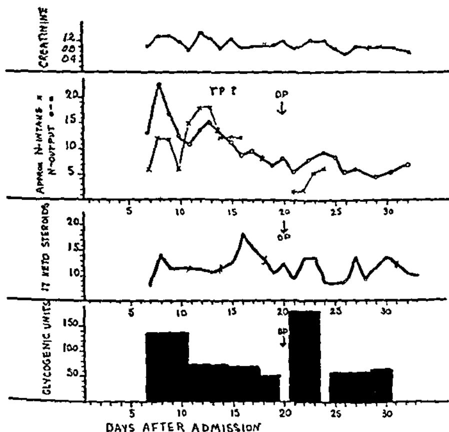
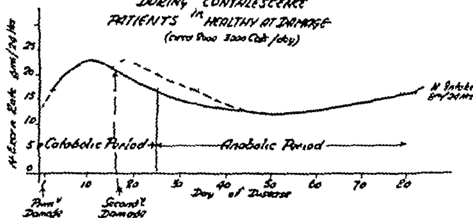


FIG 5 Case No 127 (Dol) Male 45 ulcers gastric carcinoma

In Fig 8 are the data relating to an individual who is chronically ill dying in fact of gastric carcinoma and who is cachectic Here you see terminally a marked rise in the urinary corticoids to 200 glycogenic units per day a marked rise in keto steroids and a marked rise in urinary nitrogen excretion This is the sort of evidence upon which the conclusion was based that the corticoids and urinary nitrogen run more or less parallel

The data in Fig 9 on the other hand, are those of an individual

with chronic tuberculosis, in whom, as we usually find, the urinary corticoid excretion is comparable to those of a normal individual (I will not say adequate for the person but within normal limits) He had a first stage thoracoplasty on day 35 There is a fall in nitrogen



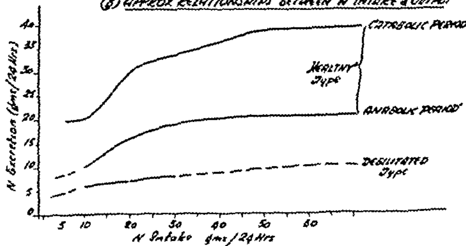
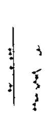
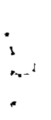
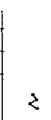


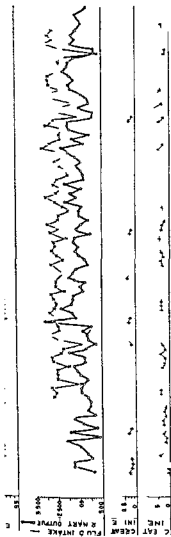
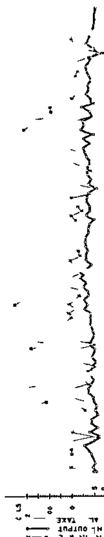
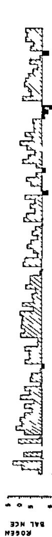
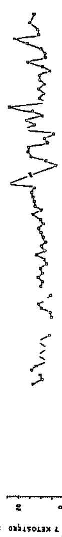
Fig 6

intake which leads to a negative nitrogen balance but absolutely no rise of urinary nitrogen, in spite of the level of 300 glycogenic units of urinary corticoid excretion being attained post operatively

In other words here is a variation from the usual pattern in that the adrenal cortex responded with no effect on nitrogen excretion

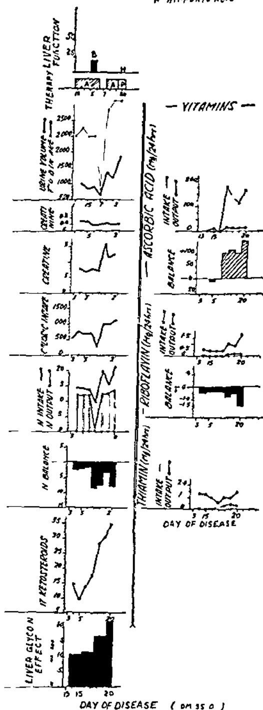



Fig 8 Case No 125 (RYA) Male 44 WGT 92 lbs gastric cachexia carcinoma

If you had given this individual ACTH he might have responded in a similar way, but in this case there is a dissociation between the response of the adrenal and the response of the urinary nitrogen excretion The two do not run parallel in all cases and they are not necessarily correlated In other words not only is the amount of

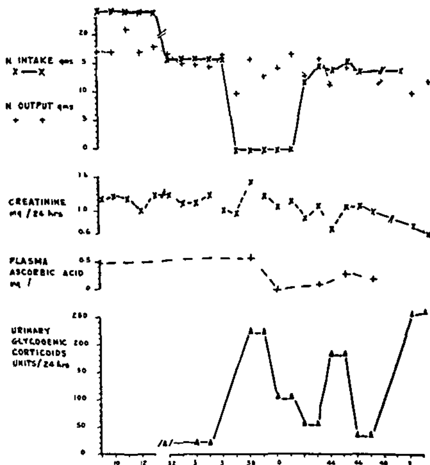


Fig 9 Case No 283 (Mar) Pulmonary tuberculosis

adrenal hormone produced important but also the total metabolic status of the person which may involve a great many different factors and the individual may not respond either to injection of ACTH or to spontaneous liberation of cortical hormones in this instance in the same way as does a normal person

In Fig 10 are the data of a case of rheumatoid arthritis Ordinarily we think of the nitrogen balance being related to weight gain in terms of nitrogen times about 27 with no water storage from the exterior

accompanying the protein deposition In this case the weight gain is in accordance with the ratio N times 6 25

The data in Fig 11 concern a case recovering from fever of unknown origin where the actual weight gain is parallel to N times 27

In other words one does not always get the same response to stress What the reason is for these different responses of people who are

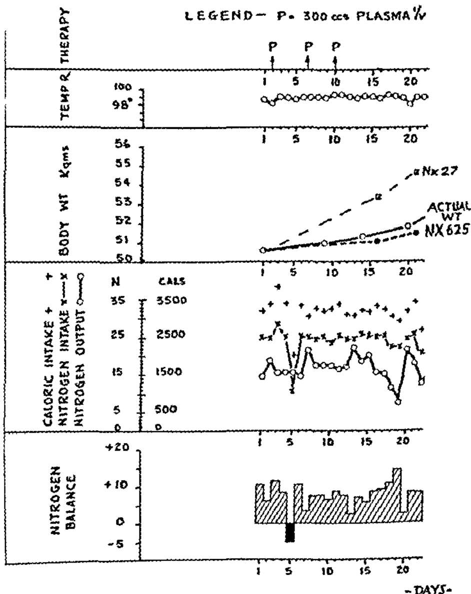


Fig 10 Case No 207 (Thom) Male, 37 (rheumatoid arthritis) P = 300 ccs Plasma 1/v

chronically ill in their weight gain relative to their nitrogen balance I do not know

From the above and some other papers presented at the Conference it is apparent that the effect of stress upon an individual may be quite varied The stress may fail to fire the adrenal at all because of a failure at the hypothalamic level at the pituitary level at the adrenal level itself or the amount of adrenal hormone liberated may be greater or less to a given environmental agent depending upon the state of these various organs Once the adrenal hormones have been liberated their effect upon metabolism and upon the body in general will be dependent upon the general and metabolic status of the body at the time the adrenal secretes its hormones

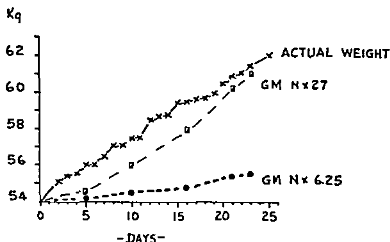


Fig 11 Case No 176 (Ross)

DISCUSSION

DR L G JOHNSON We have performed nitrogen balance studies and measured the urinary corticoids in some cases of rheumatoid arthritis

The first case (Fig 12) is that of a 38 year old male who had an acute attack of rheumatoid arthritis with psoriasis While on a caloric intake of 2700 to 3000 calories and a protein intake of 150 gms or 25 gms of nitrogen per day the nitrogen excretion was approximately 18 gms Relatively large quantities of nitrogen were therefore being stored even in the presence of an acute or subacute inflammatory process

During this period the urinary corticoids were above normal ranging from 125 to 160 glycogen units per day At the start of the studies the patient was bed ridden There was gradual clinical im

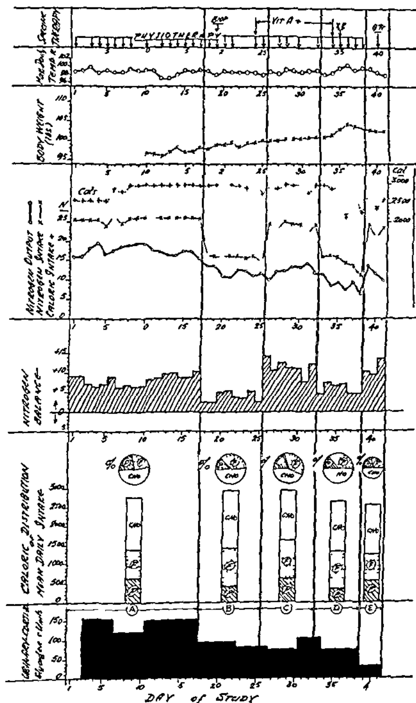


FIG 12 Case No 173 (Cass) Male 38 rheumatoid arthritis—malnutrition
Biop = Biopsy of skin taken
Vit A+ = Vit A dose Level increased
X R = X ray
G Tr = Gold treatment

provement and at the end of the studies he was able to get up for 3 hours a day By this time the corticoid had fallen to a normal level but there was little change in the rate of nitrogen excretion

The second patient (Fig 13) a 37 year old male with rheumatoid arthritis was in a positive nitrogen balance of more than 5 gms per day Urinary corticoids were above 100 glycogen units for two brief periods Starting on the fifteenth day he was given 40 mgs of methyl

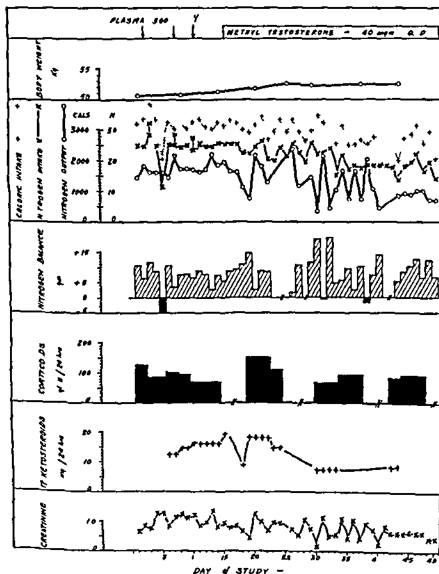


Fig 13 Case No 207 (Thomp) Male, 37 rheumatoid arthritis

testosterone daily with eventual depression of the 17 KS to about half the pre treatment level Corticoids were also lowered at the same time which may or may not have been due to the effect of methyl testosterone This patient showed no clinical improvement throughout the period of study

A 59 year old male (Fig 14) with severe rheumatoid arthritis of

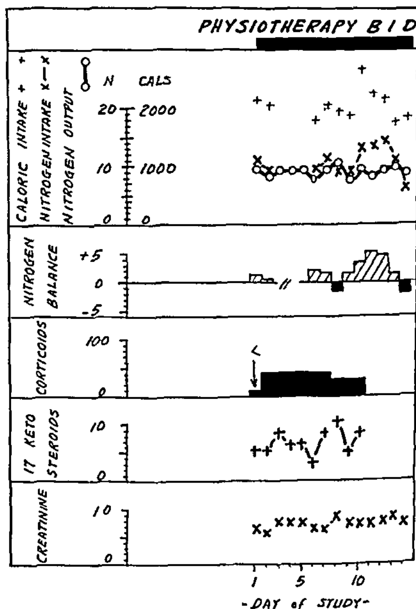


Fig 14 Case No 256 (Wint) Male 59 atrophic arthritis

many years' duration was studied This patient was in nitrogen equilibrium on an intake of 10 gms of nitrogen and 2000 calories There was however no rise in the nitrogen excretion when the intake was raised to 15 gms per day a positive balance being thus established Urinary corticoids were less than 10 glycogen units at the start of the study and never rose above 50 The 17 KS ranged from 5 to 10 mgs per 24 hours

A lengthy metabolic study was performed on a 51 year old male (Fig 15) with rheumatoid arthritis of 5 years duration In spite of a high nitrogen intake the rate of nitrogen excretion remained low throughout and large quantities of nitrogen were stored This phenomenon apparently continued unabated even though the patient had regained weight and was heavier than he had ever been during his life The corticoids and 17 KS were within the so called normal range These determinations were repeated 3 years later and found to be be low normal There was no marked clinical changes during this interval

The final case is that of a 24 year old male (Fig 16) with rheumatoid arthritis of 5 months duration When the metabolic study was started, both knees were very swollen with marked limitation of movement On an intake of 2700 calories and 16 gms of nitrogen the patient was in nitrogen equilibrium in spite of a fever of 100 to 101 degrees He was given 1 mg of adrenalin intravenously on each of 4 days There was immediate and marked improvement in his condition both subjectively and objectively This was accompanied by a fall in the nitrogen excretion with a resultant positive balance of 3 to 4 gms per day 17 KS showed no rise but rather a slight fall An attempt was made to measure the corticoids but unfortunately the extracts were toxic to mice

In summary metabolic studies on 5 cases of rheumatoid arthritis have been presented all of whom with the exception of the last case showed a decided tendency to store nitrogen In 2 cases the corticoids were higher than the usual normal range and in 2 cases they were low or at the lower limits of normal There was no correlation between these findings and clinical improvement

DR WILLIAM PARSON (University of Virginia Hospital Charlottesville) Some studies were done as part of a collaborative effort at Tulane University with respect to alterations in nitrogen metabolism in Cushing s Syndrome and following the administration of ACTH to a normal male

This work verified the type of excretion curve seen following the administration of isotopic stable nitrogen N 15 incorporated into glycine in the diet of normal individuals (Fig 17)

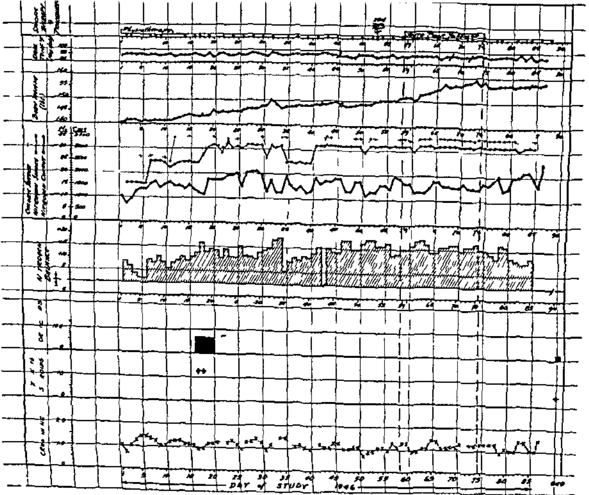


Fig 15 Case No 185 (Haml) Male 51 arth t s ight]

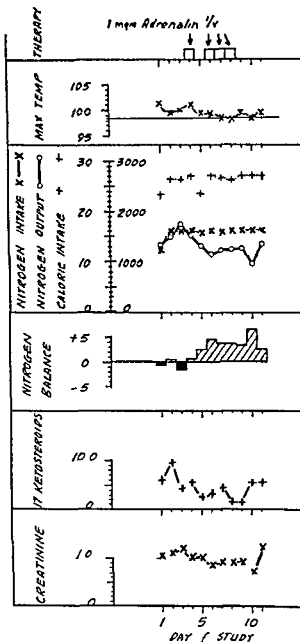


Fig 16 Case No 280 (D All) Male 24 years rheumatoid arthritis—atypical

You see 3 uninterrupted line curves the bottom one low protein diet then normal then high protein The per cent of the fed N 15 which is excreted is shown here These studies were done on a metabolic regime wherein the normal individuals were in nitrogen equilibrium while on the various diets

The excretion of the tagged nitrogen is high on a high protein, as seen there We administered ACTH in doses of 25 mgs every 3 hours for 6 doses The first doses were given starting 6 hours before the tag glycine was given This individual had a classical response to ACTH with a negative nitrogen balance of 6 grams in two days hav

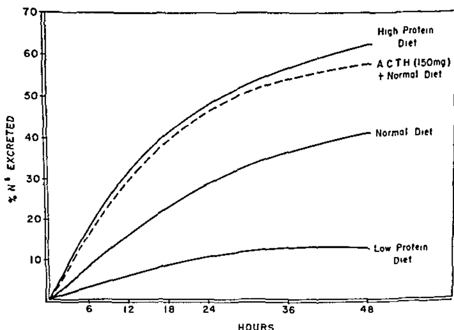


Fig 17

ing been in nitrogen equilibrium prior to administration of ACTH

Fig 18 shows the curve seen in a patient with Cushing s Syndrome who was in nitrogen equilibrium at the time, on a normal diet This curve is similar to that of the normal individual on a normal diet who has received ACTH When the patient with Cushing s Syndrome achieved a positive nitrogen balance on testosterone propionate the curve became similar to that of the normal individual on a normal diet

I think that is of considerable interest in view of the fact that Dr Browne has commented on nitrogen equilibrium in his patient as an index perhaps of normal nitrogen metabolism following injury

It is clear that profound alterations in nitrogen metabolism may

occur without reflection in the overall classical nitrogen balance studies

I might say that we are very hesitant to draw too many conclusions from this type of work Mathematical analysis of the data has been made I think tentatively we might say that these observations would fit in with the concept that following the administration of ACTH and in Cushing s Syndrome there is decreased anabolism of protein

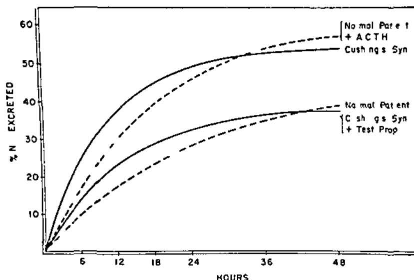


FIG 18

POST CONFERENCE DISCUSSION BY DR J S L BROWNE, MONTREAL, CANADA

The following written after the Conference is an attempt at an explanation of the above findings and to fit together some of the facts learned at the Conference with the previous work at the University Clinic

What I propose to put forward now is a hypothesis it is in fact a speculation and is valid only insofar as it leads to future work First of all one or two more facts It was found by Dr Ragan and his group that if a biopsy is done in the case of rheumatoid arthritis treated with ACTH the biopsy wound heals only slowly Further when Dr Selye injects formalin into the foot of the rat ordinarily he gets necrosis a marked edema cellular reaction around the site of the necrosis and a tendency toward arthritis in the joints adjacent If Cortisone or ACTH is administered 3 or 4 hours before or if the adrenal is fired with exer-

You see 3 uninterrupted line curves, the bottom one low protein diet then normal then high protein The per cent of the fed N 15 which is excreted is shown here These studies were done on a metabolic regime wherein the normal individuals were in nitrogen equilibrium while on the various diets

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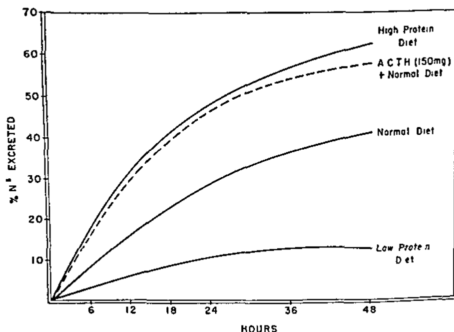


FIG 17

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I think that is of considerable interest in view of the fact that Dr Browne has commented on nitrogen equilibrium in his patient as an index perhaps of normal nitrogen metabolism following injury

It is clear that profound alterations in nitrogen metabolism may

the case of an individual who is not healthy, for example chronic bronchiectasis or other chronic illness an operation may not lead to the rise in urinary nitrogen excretion Furthermore as studied by Dr Schenker, Johnson and Hackney in various diseases including rheumatoid arthritis tuberculosis chronic bronchiectasis or chronic Friedlander s pneumonia and so on there may be a marked tendency to continuous storage of protein in the face of fever and of inadequate caloric intake As an example and referred to above (Fig 7) is the case of a woman who had a fractured jaw and a fractured femur 3 months before the study She lost a great deal of weight her fractured femur had become infected with pseudomonas and *E coli* before the days of streptomycin and her temperature was 100° to 101° F She was 3 months later on 800 calories with a nitrogen intake of 6 grams which is 36 grams of protein daily Her urinary nitrogen excretion was 4 grams so she was in slightly positive balance on this extremely low intake in the face of fever and when her intake was raised to 17 grams of nitrogen daily she was in 12 grams of positive nitrogen balance The urinary nitrogen excretion did not rise and the N P N did not rise so it was not a matter of kidney retention it was a matter of the body holding on to all the protein it could get with an intense mechanism for storing and holding and restoring the protein so that the body does not use any of it for energy purposes

Another example is a man who 26 days after bilateral fracture of the femur was in equilibrium at 16 grams of nitrogen intake and 2700 calories Now it will be said that since he was in equilibrium on this intake he was a normal person because that is the status of a normal person However when his intake was raised to 32 grams of nitrogen and 3700 calories again his urinary nitrogen excretion rose only slightly and he went into marked positive balance After he gained considerable weight he was put on his previous diet and then again his nitrogen intake was raised in the same way exactly to the same level but in this instance the urinary nitrogen excretion now rose In other words in this particular case as the protein of the body was restored this homeostatic mechanism for the retention of protein by the body diminished

However Dr Johnson and Dr Hackney find that in more chronically ill people the tendency to store nitrogen may go on for long periods of time—in the woman in Fig 7 it was still going on a year later Furthermore as mentioned Dr Johnson finds another peculiarity in chronically ill persons The ordinary classical relationships of storage of nitrogen to gain in body weight is that for each gram of nitrogen there is 27 grams of body weight gained which has always been taken as standard and as nitrogen balance becomes positive weight should go up along this N times 27 line On the other hand

cise or any other method 3 or 4 hours before the necrosis occurs of course, from the fixation but there is only minimal edema and cellular reaction In other words the local reaction of the body to damage is affected as well as the general reaction

Furthermore certain studies were brought forward in discussion by Parsons with regard to the metabolism of N 15 glycine which are pertinent If one measures the per cent of the N 15 (administered as glycine by mouth) which appears in the urine as urea in 24 hours in a normal person on a moderate protein intake about 28% is excreted in 24 hours (See Fig 17) In an individual on a high protein diet 60% is excreted in 24 hours This is easy to understand because there are more total amino acid molecules and more total protein molecules so each of them has less chance of being held in the body

In Cushing s syndrome on a moderate protein intake and in overall nitrogen equilibrium the value is 60% (See Fig 18) In other words in Cushing s syndrome although the individual may be in nitrogen equilibrium each molecule has less chance of being included in the body These observations fit well with the view produced by Albright and ourselves concerning the S hormone Dr Albright believed that this hormone is antianabolic whereas we considered it to be catabolic or in other words tended to increase breakdown of the protein of the body or lessen its chances of being rebuilt

The above illustrates an extremely important point namely, that an individual may be in nitrogen equilibrium and yet the status of the protein metabolism may not be normal Thus, if testosterone propionate is administered to a case of Cushing s syndrome N 15 excretion value returns to 28% (see Fig 18) whereas if ACTH is administered to a normal individual the N 15 excretion value shifts to the Cushing level and yet both of these individuals may be in nitrogen equilibrium

When the studies of nitrogen metabolism were being performed in the University Clinic at the beginning of the war it was found that a *marked increase in urinary nitrogen occurred in previously healthy* people acutely traumatized and Dr Victor Schenker called this the catabolic state This occurred whether the individual had an operation fracture or burn although the degree might vary according to the intensity of the trauma and according to the response of the person Over a period of time—a 2 to 3 week period—the level of the nitrogen fell again and the anabolic state occurred

My *mind is still conditioned by the high urinary nitrogen* excretion that occurred although we now know that it would be possible for catabolism or antianabolism to occur without a rise in urinary nitrogen excretion in view of the N 15 data presented by Dr Parson

On the other hand Dr Schenker and Dr Johnson found that in

son, is not very great, in the presence of a high "S" hormone secretion, the wound may fail to heal as has been demonstrated in the case of rheumatoid arthritis Now as this condition passes off the wound becomes anabolic relative to the rest of the body, and becomes capable of collecting protein before the rest of the body swings over into the other state which I shall describe in a moment, consequently amino acids are transferred into it and the wound heals

If the wound fails to heal because of infection or for any reason until such time as the nitrogen metabolism has swung over to what is called the anabolic state or more particularly into what we have described as the debilitated state (as illustrated in Fig 7) then the body says, all right you ve had your chance now I ve got to have it back again and all the tissues begin to grab, why I don t know Consequently there is much less to go around and each part of the body gets less particularly if the individual is on a low intake The amount of amino acids coming to the wound is inadequate consequently it does not heal

Now you will recall that there was a therapy in the old days of intramuscular blood and milk for chronic wounds which did not heal I submit that the mechanism of this was to refire the adrenal and to remobilize or make mobilizable the body protein but you say when you thus fire the adrenal in chronic illness there is no rise in urinary nitrogen—why is that? I would remind you that in pregnancy there is no negative nitrogen balance no rise in urinary nitrogen yet corticoids are extremely high in pregnancy as Dr Venning has demonstrated The reason I think is because there is a marked and strong anabolic focus within the body the fetus and the uterus are growing consequently they grab all the amino acids as they go around and they are not deaminized to appear in the urine so then the rise of urinary nitrogen is a reflection of the differential between the transfers of protein within the body

You are aware that Whipple s group in Rochester demonstrated that if one performs plasmaphoresis in a dog 58% of a good biological value protein administered in the food appears as plasma protein Now if one does not plasmaphorese 58% doesn t appear as plasma It is only when you are removing a tissue as you can do in the case of plasma that you deviate the body s homeostatic mechanisms into the formation of more of that particular tissue Similarly in the case of phlorhizin 58% of the fed amino acids is deviated into glucose but that is only when the glucose is being drawn out

Most of the attention in this regard has been fixed on the external sources of protein in the food I submit that the internal body sources in terms of Whipple s own theory are extremely important because he regarded them as freely interchangeable with the plasma proteins

Dr Johnson has found that in many of these chronically ill people the weight gain is at the rate of times 6 25 and not N x 27 indicating that either water is being obtained by internal transfer within the body or that the protein is being deposited either extracellularly or intracellularly in increasing concentration in the cell or in the extra cellular space

We know furthermore that various tissues have various capacities for holding protein We know that in starvation the heart and the brain tend to retain their protein much longer than the other tissues in the body, the liver yielding it very readily, the muscles perhaps less readily but the relative capacities to hold protein between these not being very clearly known

The speculation formed from all this is as follows that the tele ological reason for this sudden breaking down of protein (which, in my opinion and in Dr Albright s opinion, was conditioned and brought about by the rise in the secretion of the S hormones which has been demonstrated in the urinary excretion by Dr Venning) was a shaking loose and rendering more easily mobilizable the proteins of the body and I expected the urinary nitrogen to rise This occurred and in the first studies we found that there was a distinct parallelism between the rise in urinary nitrogen as I pointed out and the rise and fall of the urinary corticoids and that was satisfactory

As time went on however we found that corticoids could be very high and the urinary nitrogen be low relative to the intake with the individual still in positive nitrogen balance One of these conditions is pregnancy Furthermore, as mentioned, Dr Hackney has recently demonstrated that in a case of chronic tuberculosis (Fig 9) after first state thorocoplasty the corticoids rose to 300 glycogenic units per day whereas the urinary nitrogen excretion remained completely un altered So with these studies and others the theory of Albright and ourselves on the direct correlation between the S hormone as it was called then, and nitrogen metabolism has not been maintained Dr Mackenzie has demonstrated that the adrenal is necessary for this rise in the rat which was first demonstrated by Cuthbertson but in man there was some doubt about it

To return then to the teleological function the body breaks down or shakes loose protein for the purpose of supplying protein building blocks to the wounded area The body does not distinguish whether the wound be from a pneumococcus or from a cut or a burn it says in effect go ahead you need to be rebuilt take the building blocks, so tissues begin to break down or if they do not break down the protein is 'loosened That is a phrase which I coined the best phrase I could think of in those early days The wound takes part in this also and if the total intake or body supply of protein as in a chronically ill per

fibrosis one into tuberculous granuloma, and so forth depending upon the environmental agent and the special reactions of the body to that agent but the capacity for these tissues to build up depends essentially upon their capacity to capture protein

I consider that the general aspect which tends to favor the formation of these abnormal tissues is the anabolic tendency which we have seen in the variety of chronic disease states as illustrated by the continued retention of nitrogen ACTH or Cortisone remobilizes the protein, facilitates protein transfer away from the abnormal tissue either with or without rise of urinary nitrogen These abnormal tissues are relatively weakly anabolic One should remember that most of these people have lost weight so that the normal tissue is all ready to grab if anything is shaken loose

Now this is perhaps further illustrated by the finding by Ishmael Hellbaum, et al that testosterone propionate in high doses of 300 milligrams plus Δ^5 pregnenelone or even testosterone alone affects rheumatoid arthritis Dr Palmer Howard has treated one patient and after 6 days the patient who couldn t walk for 6 years got up and walked much the same as in the treatment with Cortisone but the effect is slower Dr Venning demonstrated on the other hand that testosterone propionate depresses the production of the S' hormone and Parsons has just shown that it tends to cause the N 15 to move towards normal How can one account for this effect on the basis of this speculation? I consider that what may have happened here is that the testosterone causes the muscles shall we say for the sake of argument to be relatively more anabolic than the abnormal tissue and consequently to capture the protein from it Again an internal transfer of protein I again state that this is a pure speculation I think then that one can fit together perhaps the whole picture along those lines to lead of course to further investigation Internal transfers of sodium water potassium etc may also occur and account for the variety of overall balances negative or positive found after ACTH and Cortisone administration under different conditions

Hawkins, et al, found that when a turpentine abscess was made in a dog much more plasma protein appeared from a given food, that is in my opinion because the turpentine fired the adrenal mobilized the body protein and some of that as well as the food protein appeared as plasma In other words the body protein was more easily deviated

In the case of pregnancy then the anabolic focus is great and the body protein loosened under the influence of the adrenal cortex The maternal protein is transferred into the fetus If the mother has an inadequate protein intake or caloric intake the fetus still grows and the mother drains her protein into the fetus One can see now why there need not be a rise in urinary nitrogen

If there is a relatively small anabolic area in the body as in the case of a perfectly healthy person who has no need to rebuild his tissues and he is acutely traumatized, the proteins are loosened and the body just sweeps away the excess which isn t taken up by deaminizing amino acids and excreting the nitrogen as urea but if there is any place where these amino acids are being grabbed off then internal transfers occur and in the overall nitrogen balance this is not detected

One recalls seeing rats with rapidly growing tumors These can be *in overall positive balance and yet one can watch the body proteins* of the animals being drained into the tumor in spite of the fact that the overall creature is in positive nitrogen balance I consider then that the capacity to capture protein the relative anabolic capacity of tissues is extremely important in terms of their growth I consider that under high S hormone secretion the body s proteins are more readily mobilized Where they will be transferred and the relative transfers which will occur will depend upon the metabolic status—the total status of the body and the level of the S hormone

It has always seemed to me that this loosening of protein was illustrated by Selye s and others findings of gastro intestinal erosions in acute states Here you have a loosening of a body tissue That particular tissue is in contact with proteolytic enzymes so it dissolves What I mean by loosening I cannot tell you—I don t know except that it connotes less capacity to build in protein as demonstrated by the N 15 *tissue studies* because in Cushing s *syndrome* wounds do not heal well either

Further, I consider that the granulomas and fibrosis of tuberculosis the fibrosis of cirrhosis the collagen deposition of various diseases as super *or malignant healing They are the result of the* capacities of these tissues to seize protein for long periods of time The special aspect of these diseases of these processes I should say is determined to my mind by a variety of factors which makes one into periarteritis nodosa, one *into rheumatoid arthritis one into cirrhotic*

(c) Cells in the median eminence influenced by this tract are postulated to produce a secretion which is then carried to the adeno hypophysis by the hypophysial portal system of veins which drains from the median eminence down into the pars tuberalis

2 The autonomic nervous system (a) Sympathetic nerves from the cervical chain pass to the carotid plexus the circle of Willis and hence down the stalk to the pituitary Since the hypothalamus exerts a control over the sympathetic nervous system it was felt that it might

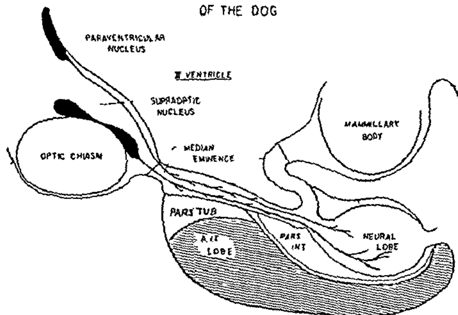


Fig 1 The outlines of the paraventricular and supraoptic nuclei have been projected onto the midline

influence the adenohypophysis in this way (b) Parasympathetic fibers join the carotid plexus from the greater superficial petrosal nerve and may reach the adenohypophysis These fibers apparently have little effect on pituitary function however

3 Scharrer[4] has described the cells of the paraventricular and supraoptic nuclei as being secretory cells with granules which can be seen in different phases of a secretory cycle These cells are surrounded by a rich vascular network and are perforated by endocellular capillaries so that anatomically it would seem that they might secrete a hormonal substance directly into the blood stream Our work seems most in accord with this last theory

11

The Relationship of the Hypothalamus to Pituitary-Adrenocortical Function*

David M Hume and George J Wittenstein

SURGICAL SERVICE OF THE PETER BENT BRIGHAM HOSPITAL AND THE SURGICAL LABORATORY OF THE HARVARD MEDICAL SCHOOL BOSTON

The factors responsible for the release of ACTH from the anterior pituitary following stress have been studied in dogs Although this work is still in progress and certain aspects of it are incomplete and inconclusive as yet we believe we have shown (1) that the intact hypothalamus is essential for the normal release of ACTH and adrenal corticoids in response to stress (2) that lesions in the hypothalamus abolish or markedly decrease this response even in the presence of an intact pituitary and adrenal cortex and (3) that this effect is mediated by means of a hormonal mechanism [1]

As a measurement of increased secretion of ACTH and adrenal corticoids the fall of circulating eosinophils has been employed Epinephrine insulin and operative trauma under ether or nembutal anesthesia have been used as stressing agents

Many investigators have studied the problem of neural especially hypothalamic, control of anterior pituitary functions usually using lactation growth gonadal or thyroid activity as a measure of this control This entire problem has recently been the subject of an excellent review by Harris [3] Several views are held as to possible routes by which the hypothalamus can exert control over the anterior pituitary

1 The hypothalamico hypophysial tract which is composed mainly of fibers from the supraoptic and paraventricular nuclei descends into the neural lobe (Fig 1) This tract has been postulated to influence the anterior pituitary in one of the following 3 ways (a) Fibers have been described which pass from this tract into the pars tuberalis and other portions of the adenohypophysis and which are thought to have a direct secreto motor function These fibers are not present in all species studied however (b) Secretions of the neuro hypophysis, which are controlled by the hypothalamico hypophyseal tract are said to affect the secretory cells of the adenohypophysis

* Supported by a grant in aid for research from the Commonwealth Fund

VI Extracts were made of beef hypothalamus cerebral cortex and cerebellum, and these extracts were then injected into dogs with hypothalamic lesions who had shown absent or sub normal re sponses to two or more of the various stressing agents tested

RESULTS

1 Severing the stalk had no effect on the normal eosinopenic response to stress (Fig 2) The hypophysial portal system of veins was

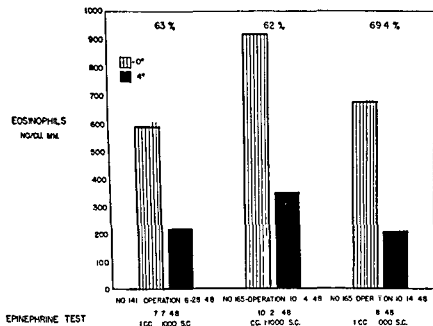


FIG 2 Epinephrine test in stalk section dogs in which a piece of polyeth ylene film has been placed between the pituitary and the hypothalamus Note the normal eosinopenic response to this stress

interrupted and the pars tuberalis was completely stripped from the median eminence The rostral half of the median eminence was in tact however

2 Removing the posterior lobe had no effect (Fig 3)

3 The animals continued to respond in a normal fashion even with all the posterior and over half the anterior lobes gone When al most all the pituitary was removed the response was decreased 50% but was still present

4 Complete hypophysectomy completely abolished the response

METHODS

I Several series of operations were done on the pituitary after it had been exposed either by the transtemporal or transbuccal approaches usually the former

1 The stalk was severed through the median eminence, and a piece of polyethylene film was placed between the pituitary and the hypothalamus to prevent regrowth of nervous and vascular connections between the two
2 The posterior lobe was removed leaving the anterior intact
3 Varying portions of the anterior and posterior lobes were removed up to a sub total hypophysectomy leaving only a small portion of adenohypophysis including the pars tuberalis
4 Complete hypophysectomy was done

II Electrolytic lesions were made in the hypothalamus and adjacent structures either at open operation after exposure by the trans buccal or transtemporal routes or later, by a special stereotaxic instrument made for use in the dog

1 Bilateral lesions were made in the supraoptic nuclei producing diabetes insipidus
2 Paramedian lesions were made in the anterior hypothalamus and at the junction of the middle and posterior hypothalamus
3 Bilateral lesions were made in the lateral hypothalamus

III The cervical cord was severed at C7 and the animal was allowed to recover An operation was then done below the level of section to determine the response of the pituitary to this stimulus

IV Small coils were encased in lucite shells one end of the winding being connected to a platinum wire insulated except at the tip with a glass capillary and the other to a stainless steel indifferent electrode These units were then implanted in the head with the stereotaxic instrument in such a manner that the tip of the needle lay in the hypothalamus and the coil plugged tightly into a stainless bushing which was screwed through the skull The skin was closed over the coil This technique was modified after that used by Harris in rabbits The dog s hypothalamus could then be stimulated at any time with the dog fully conscious by bringing a large primary coil close to the dog s head and inducing a 60 cycle current in the implanted coil This procedure was carried out

1 In normal dogs
2 In completely sympathectomized dogs

V Identical abdominal operations were done as stressing procedures in different animals and in the same animal at different times, under ether anesthesia in one case and nembutal anesthesia in the other

ANTERIOR HYPOTHALAMIC LESION

DOG NO 28 49

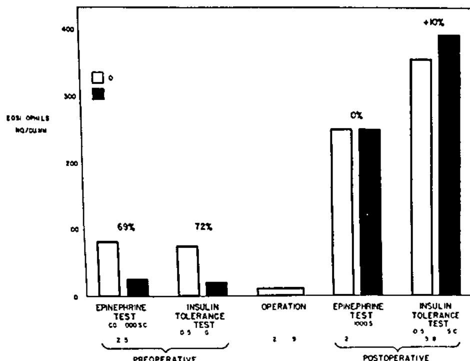


Fig 4 The per cent fall of circulating eosinophils in response to epinephrine and insulin before and after a paramedian anterior hypothalamic lesion Note the increase in the zero hour eosinophil count following the lesion

7 Lateral or unilateral median hypothalamic lesions had no effect on the normal response to stress

8 After sectioning the cervical cord and allowing the animal to recover an epinephrine test was done to determine the reactivity of the pituitary adrenocortical system When this system was found to be reactive an operative procedure was carried out below the level of the section (Fig 7) This operation produces an eosinophil fall of 80–90% in normal dogs In the cord section dog no eosinophil fall occurred

9 When remote control stimulation of the hypothalamus was carried out in normal dogs (Figs 8 9 10) a marked eosinophil fall occurred together with a concomitant leucocytosis (Fig 11) This was more marked on stimulation of the anterior hypothalamus than of the posterior The possibility remained that this fall might be due to released epinephrine although this seemed unlikely because there was no change in the blood sugar during the period of the test However

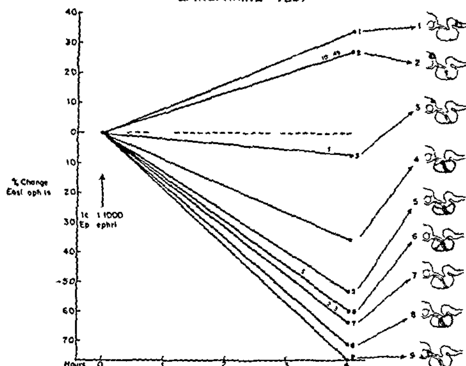


FIG 3 The per cent change in circulating eosinophils 4 hours after the injection of 1 1000 epinephrine s c Dogs 1-3 paramedian hypothalamic lesions Dogs 4-6 varying amounts of anterior and posterior lobes removed but no hypothalamic lesions Dog 7—normal dog Dog 8—posterior lobe only removed Dog 9—bilateral hypothalamic lesions involving supraoptic nuclei and producing marked diabetes insipidus The shaded areas show the approximate extent of the lesion or excised area

5 Lesions in the supraoptic nuclei did not alter the response

6 Paramedian lesions in the anterior hypothalamus and at the juncture of the middle and posterior hypothalamus abolished the usual response to epinephrine and insulin and decreased the response to operative trauma A typical animal is shown in Fig 4, and a summary of results following these lesions is shown in Fig 5 In one instance the response to operative trauma as well was completely abolished These animals differed from hypophysectomized animals in the following ways

a There was no gross atrophy of pituitary target organs

b There was slight or no insulin sensitivity

c They continued to react to test doses of ACTH whereas the hypophysectomized animals rapidly developed atrophy of the adrenal cortex and no longer reacted to a single injection of ACTH (Fig 6)

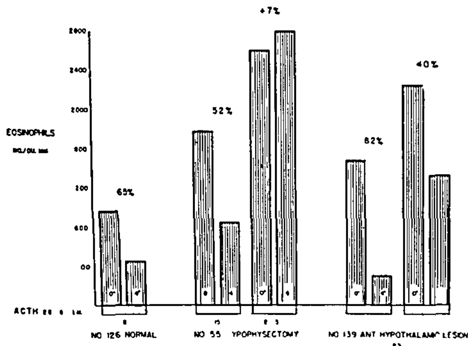


Fig 6 After hypophysectomy the adrenal cortex atrophies so that it is no longer responsive to a single injection of ACTH This may take place in 7 days if the hypophysectomy has been complete After a hypothalamic lesion which abolishes the response to stress the animal continues to react to a single injection of ACTH indicating that the adrenal cortex has not undergone marked atrophy but that the animal is incapable of producing an increased secretion of ACTH in response to stress

factor in the release of ACTH from the pituitary This is further supported by the fact that nembutal decreases the eosinopenic response following trauma in the normal animal The barbiturates have been shown to have a selective inhibitory effect on hypothalamic nuclei [6] Dogs with hypothalamic lesions show no gross adrenal cortical atrophy and continue to respond to ACTH This suggests that the anterior pituitary continues to put out maintenance doses of ACTH (although at a lower than normal level as shown by the increase in zero hour eosinophil count), but is incapable of increased secretion in response to stress Sectioning the nervous and vascular connections between the intact hypothalamus and pituitary does not abolish the eosinopenic response to stress so that the hypothalamic control of pituitary release of ACTH must be mediated by a humoral mechanism employ

to rule this out, coils were implanted in animals which had previously had total sympathectomies Fxactly the same results followed stimulation of the hypothalamus in these dogs

10 Abdominal operations done under nembutal anesthesia are followed by a markedly decreased eosinopenic response as contrasted to identical operations under ether anesthesia

11 Preliminary work with hypothalamic extracts tends to show that these extracts are capable of producing release of ACTH from

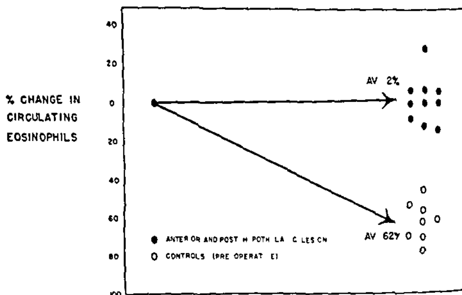


FIG 5 The per cent change in circulating eosinophils 4 hours after the injection of 1 cc 1 1000 epinephrine s c before and after the production of paramedian hypothalamic lesions Two animals had no pre operative tes s

the pituitaries of animals whose hypothalamic lesions prevent or modify the normal release following non specific stress This work is not completely conclusive as yet however

DISCUSSION

The normal eosinopenic response to non specific stressing stimuli is mediated by secretions of the adrenal cortex which are under the control of ACTH released by the anterior pituitary Since this response is abolished or markedly modified by making small electrolytic lesions in the hypothalamus the hypothalamus must be an important



Fig 9 X ray of dog #226 with the secondary unit implanted The tip of the insulated platinum wire lies in the hypothalamus

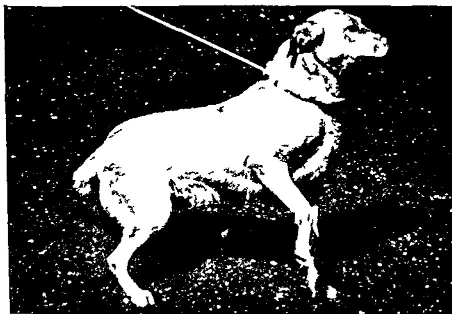


Fig 10 Dog #226 3 months after the implantation of the coil

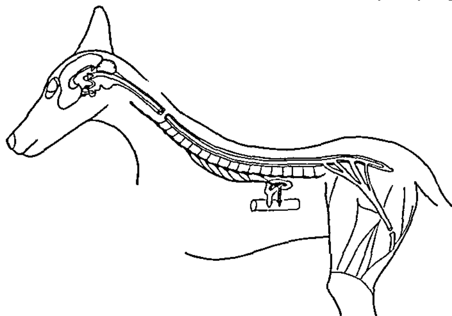


Fig 7 Section of the cord at C-7 Following section of the cervical cord the animal no longer shows the normal eosinopenic response to operative trauma in the hind limb

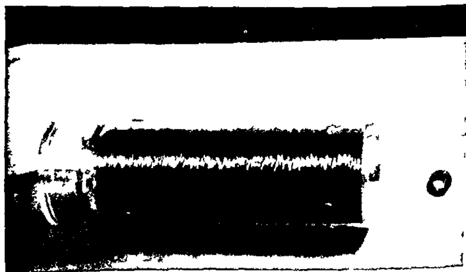


Fig 8 The coils used for remote control stimulation On the left the primary and on the right the secondary which is implanted

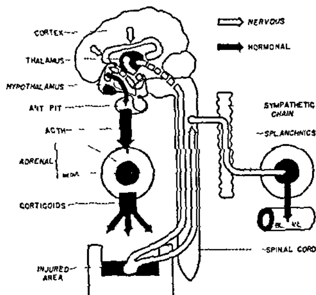


FIG 12 Diagrammatic representation of the pathways involved in increased secretion of ACTH by the anterior pituitary following trauma dotted lines represent as yet uninvestigated pathways The route invo the splanchnics leads to release of epinephrine which can then act dir on the hypothalamic center This is of secondary importance and is nc sential to the normal eosinopenic response to trauma or stress

with extracts of beef hypothalamus seems to indicate that some cific substance is formed in the hypothalamus for this purpose

CONCLUSIONS

1 An intact hypothalamus is necessary for the increased rel of ACTH from the pituitary following stress

2 This hypothalamic control of the pituitary seems to be on a monal basis

3 Following operative trauma the release by the pituitary c increased amount of ACTH is dependent upon an intact nervous nection between the injured area and the brain

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ing the general circulation for transport In the intact animal marked eosinopenic response follows operative trauma, but this response is completely abolished by sectioning the cervical cord Hence afferent nervous impulses from the injured area to the brain are essential for the release of ACTH from the pituitary following trauma General ether anesthesia does not alter this response, so it is apparently on a sub cortical level Nembutal does alter it as previously stated, prob

DOG NO 173 - COIL IMPLANT

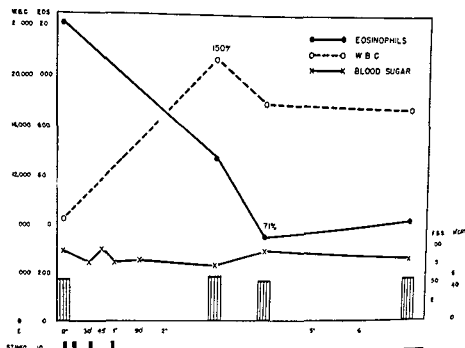


Fig 11 Anterior hypothalamic stimulation The changes in the leuco cytes eosinophils blood sugar and hematocrit following 4 three minute stimulations over the course of 1 hour in the conscious dog are charted Note the marked eosinopenic response

ably at a hypothalamic level Complete sympathectomy does not alter the response, so that neither epinephrine nor sympathetic fibers to the pituitary are essential to pituitary release of ACTH following stress Remote control stimulation of the intact hypothalamus produces a marked release of ACTH from the pituitary (even in a sympathec tomized animal) It seems reasonable to postulate, therefore that nervous impulses from the injured area end in hypothalamic stimula tion followed by release of a humoral substance from the hypotha la mus which in turn stimulates the pituitary (Fig 12) Preliminary work

DR PETER H FORSHAM Since Dr Hume is a surgeon, may I ask if in a given operation the mortality is higher with spinal than with general anesthesia?

DR DAVID M HUME I am sure I don t know the answer to that question Most people who are given spinal anesthesia are also given either epinephrine or ephedrine at the same time Probably it is not a good thing in patients with shock unless some precautions of that type are taken

DR FRANCIS D MOORE When the spinal anesthesia wears off the afferent pathways of course are activated and the whole mechanism is put into action

DR ROY HERTZ (U S Public Health Service National Institutes of Health, Bethesda Md) I might point out that this phenomenon of activating the pituitary through a peripheral sensory stimulus has been well recognized in relation to the production of gonadotrophic hormone substances particularly in the induction of pseudo pregnancy by stimulation of the cervix and in the case of ovulation in such forms as the rabbit which ovulates only after copulation This excellent study then represents an extension of that prior knowledge of the nervous control of the pituitary to the adrenotrophic phenomenon

DR DAVID M HUME That is very true I meant to mention that this method of remote control stimulation has been taken directly from Harris work on the rabbit in which he showed us that

DR R A CLEGHORN I don t see how Dr Hume has ruled out the passage of an alleged secretion from the nuclei through the hypophysial portal system

DR DAVID M HUME Because in the stalk section dogs the hypophysial portal system is cut and a piece of polyethylene film is put between the hypothalamus and the pituitary to prevent regrowth of this system These animals continue to show the normal eosinopenic response to stress in spite of the absence of the hypophysial portal system

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DISCUSSION

DR J S L BROWNE Dr H McIntosh in the Neurological Institute at Montreal has followed with ACTH testing persons who have had lesions in the hypothalamus such as suprasellar craniopharyngiomas with intact diaphragma sellae and apparently intact pituitaries in terms of absence of gross morphological destruction who show a failure of response to ACTH One cannot distinguish between a chromophobe adenoma and a suprasellar hypothalamic lesion in this way

DR DAVID HUME In that regard these were very tiny lesions not more than 1 or 2 mms in diameter so perhaps with more extensive lesions one might have a less response

DR GEORGE W THORN One interesting point in confirmation of Dr Hume s suggestion is the fact that there appears to be a difference in the response of the patient with spinal anesthesia over the patient with general anesthesia, in terms of the speed with which the eosinopenia occurs after operation suggesting clinically that *in some* patients one may not have the normal adrenal cortical stimulation until this spinal anesthesia wears off

DR ROGER A LEWIS The mechanism of ACTH production which Dr Hume has just elucidated so brilliantly may be supplemented by other pathways We have been able to produce a marked fall in the number of circulating eosinophils in man by a type of stress which may not involve an increased production of adrenalin or the hypothalamic centers and which might bring on the secretion of ACTH through increased peripheral utilization of the adrenal hormones as suggested by Dr C N H Long We found that a reduction in the arterial oxygen saturation to 70–75% was followed by a fall in the number of circulating eosinophils of about 40%

but there is no assurance that other steroids which promote sodium reabsorption may not be The subjects of this investigation were all hospitalized for close supervision of the diet and collection of specimens

In Fig 2 study was made on a 49 year old female without complicating disease Sodium intake was restricted to 8 meq per day for 12 days and then increased to 205 meq for days 13 to 33 Although the kidney responded promptly to the need for sodium retention and sodium excretion there was no discernible difference in the excretion of urinary cortin and 17 ketosteroids There was no inhibition of adrenal activity by DCA administration despite the sodium retention provoked

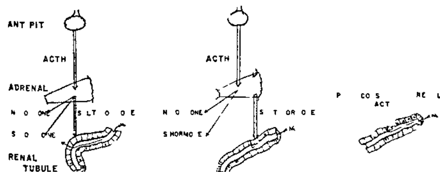


Fig 1

In Fig 3 study was made on a 46 year old female with essential hypertension and extended for a period of 94 days During the first 14 days on a diet containing 8 meq of sodium the urine contained less than 1 meq for nearly every 24 hour period Despite this remarkable sodium conservation adrenal steroid excretion was in the lower normal range At this time when presumably adrenal salt hormone should have been maximum DCA did not produce recognizable changes of steroid excretion To determine the sensitivity of our methods 54 mg of ACTH was administered over 3 days and resulted in increased excretion of both urinary cortin and 17 ketosteroids The transition from a diet with 8 meq of sodium to one which contained 205 meq was particularly interesting in this patient Nine days were required before urinary sodium excretion exceeded the intake The changes in serum sodium and potassium and fluid and sodium balances

12

Studies of Urinary Steroid Excretion During Salt Deprivation and Administration of DCA and ACTH

William H Daughaday and Cyril M MacBryde

BARNES HOSPITAL AND WASHINGTON UNIVERSITY ST LOUIS MO

Although there is general agreement concerning the existence of adrenal substances promoting the retention of sodium by the renal tubule the evidence is conflicting concerning the method of their liberation and their importance as regulators of renal tubular activity Possible mechanisms by which the adrenal might influence sodium reabsorption are presented in Fig 1 The unitarian view postulates that adrenal salt hormone is under ACTH control This view has been considerably strengthened by observing that the administration of ACTH to humans has frequently resulted in sodium retention An independent adrenal salt hormone has been postulated by the dual istic theory whereby the secretion of steroids active in carbohydrate and protein metabolism are stimulated by ACTH but that the adrenal salt hormone is secreted directly by as yet undefined mechanisms in response to sodium need It is also possible that the kidney pro vided with a constant adrenal activity is able to regulate sodium and potassium excretion and conservation

The studies to be presented have been designed (1) to compare adrenal activity under conditions of extreme dietary sodium restric tion with that of liberal salt intake (2) to determine the potency of desoxycorticosterone in inhibiting ACTH production and (3) to compare physiologic sodium conservation with the sodium retention produced by ACTH and DCA

As indices of adrenal activity we have measured urinary cortin by the method of formaldehyde liberation from partially purified urinary extracts and urinary 17 ketosteroids Although the chemical assay of urinary cortin probably measures only a small fraction of the adrenal output it has proved a useful clinical tool in comparing ad renal activity Desoxycorticosterone is not measured by the technique,

Fig. 3

Fig. 4

are presented in Fig 4 A second period of DCA administration resulted in a retention of sodium again without change in urinary steroid excretion

In Fig 5 the subject for study was a 39 year old housewife with rheumatoid arthritis Sodium intake was restricted on the fourth day to 8 meq per day The excretion of sodium fell during the next 7

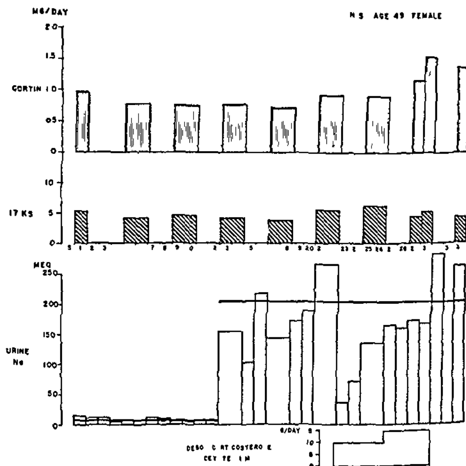


Fig 2

days until sodium balance was restored The urinary cortin and 17 ketosteroid values remained at approximately the same level Again we were able to demonstrate increases in urinary cortin and 17 ketosteroids with small doses of ACTH Later an intake of 205 meq of sodium enabled us to promote considerable sodium retention with large doses of ACTH These doses however, were associated with a 3 or 4 fold increase in the excretion of urinary cortin and 17 keto steroids

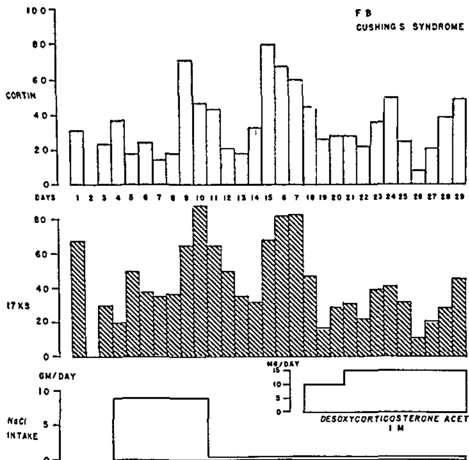


Fig 6

cretion was elevated in the presence of normal 17 ketosteroids DCA administration was followed by markedly increased cortin excretion The cause of this is not apparent but it was obvious that there is no depression of adrenal activity

From these studies we have concluded that a correlation does not exist between sodium intake and urinary steroids of the cortin and 17 ketosteroid type If maximal tubular reabsorption depends on increased amounts of an adrenal salt hormone its release is independent of ACTH and it is not measured by existing methods Conversely in humans the administration of DCA in doses large enough to produce nearly maximum sodium retention does not inhibit ACTH liberation as evidenced by unchanged excretion of urinary cortin and 17 ketosteroids The observations with ACTH have demonstrated that it is possible to detect changes in urinary steroids produced by relatively

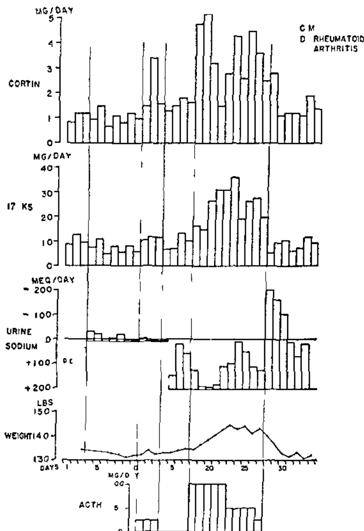


Fig 5

To study ACTH inhibition by DCA 2 patients with elevated excretion of urinary cortin were selected The first was a 21 year old woman with Cushing s syndrome The steroid excretion of this patient is presented in Fig 6 There was an elevation of both 17 ketosteroids and cortin We were interested to find the excretion not uniform but exhibited periods of much greater excretion interspersed with more normal levels DCA in this patient seemed to effect a reduction of 17 ketosteroids but no statistically significant change occurred in the excretion of urinary cortin

The second patient was a 47 year old female (Fig 7) with essential hypertension and a severe anxiety neurosis In this patient cortin ex

We have attempted to see whether this particular material correlates with the 'cortin' and the amounts are so small in terms of desoxycorticosterone acetate that we would be completely swamped. We obtain about 6 micrograms equivalent of desoxycorticosterone per day, and the total is certainly in the neighborhood of ½ to 2 or 3 mgs depending on what you are measuring.

DR JEROME W CONN This may be an example too of the lack of sufficient sodium restriction in the sense that if the individual isn't losing sodium actually in negative balance losing sodium from the body that the stimulus isn't sufficiently acute. We did experiments some years ago on conscientious objectors who were sweating in a hot room riding a bicycle every day for 60 miles and who had an average sweat volume per 24 hours of 10 to 12 liters. Under those circumstances sodium lost from the body was excessive. The urine would get down to a region where there was no chloride or sodium (or essentially none) and the largest losses of course the great losses were through the sweat.

Under those circumstances we observed marked negative nitrogen balance on adequate protein intake and increased uric acid excretion so much so that the urines precipitated the uric acid and one could see them in the gallon jugs—all these uric acids precipitated in the bottom.

Now under those circumstances where the stress was purely one calling for salt retention when desoxycorticosterone was given the individual immediately came back into nitrogen equilibrium from the negative nitrogen balance phase. Under those circumstances which were much more severe than those reported it appeared that desoxycorticosterone was able to inhibit an excessive activity of ACTH.

DR PETER H FORSHAM Are we right in talking about desoxycorticosterone as a salt retainer and other steroid hormones as salt losers?

Compound E 100 mgs a day given to an Addisonian will lead to a decreased sodium excretion in the urine and an initial out pouring of potassium. In that dosage Compound E compares quite favorably with 5 mgs of desoxycorticosterone. Obviously desoxycorticosterone is a more potent sodium retainer than is Compound E (Fig 8). This same patient on 5 mgs of DCA per day showed what we might assume to be nearly maximal sodium retention. At that point Compound E gave rise to a pardoxical outpouring of sodium rather than an additive retention of sodium (Fig 9).

One theory would be that we have probably replaced a relatively poor salt retainer on the renal tubule for a relatively very potent salt

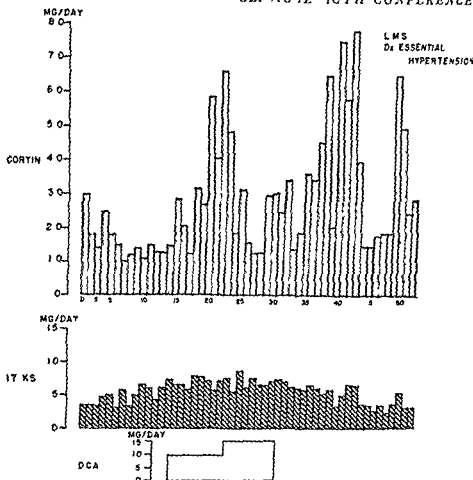


FIG 7

small doses of ACTH Large doses of ACTH may result in sodium retention but are associated with unmistakable increases in the excretion of urinary cortin

DISCUSSION

DR GREGORY PINCUS I think Dr Daughaday recognizes that the cortin measurement is very probably a measurement of a great mixture of substances and that therefore if there is a correlation between certain variables and one of these products it might very well be masked if one type of substance is preponderant over another

It is therefore very interesting to report that one can obtain from human urine in the so called cortin fractions material which will cause sodium retention apparently a steroidal substance, and it is possible to assay this in human urines

retainer if one assumes that a number of molecules of desoxycorticosterone were replaced by an equal number of molecules of Compound E one would obtain a net loss of sodium in the urine That does not mean however that Compound E is salt losing or that any of these compounds are salt losing per se Compound F appears to be a weak salt retainer Thus most effects observed in studies on man with ACTH can be explained as a change in the amounts of Compound E or related substances excreted and one does not necessarily have to invoke the presence of a specific salt retainer in man although it might exist

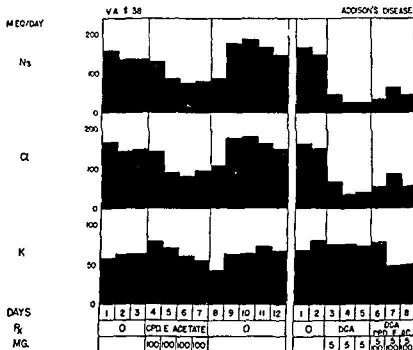


FIG 8 Effect of Compound E acetate and DCA on urinary sodium chloride and potassium excretion

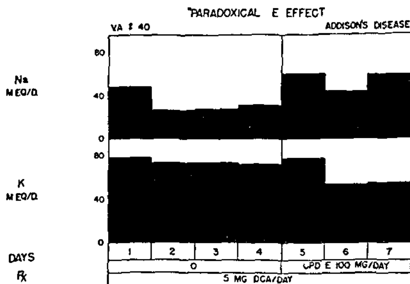


FIG 9

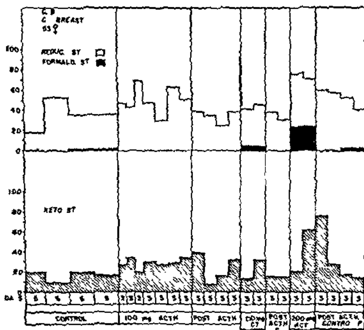

C B
C BREAST
53 ♀
REDUC ST
FORMALD ST
KETO ST
100
80
60
40
20
0
DAYS
CONTROL
100 mg ACTH
POST ACTH
POST ACTH C
POST ACTH CONTRO

FIG 2

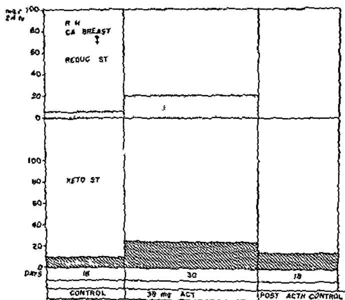

mg / 24 hr
R H
CA BREAST
REDUC ST
KETO ST
100
80
60
40
20
0
DAYS
18
30
18
CONTROL
38 mg ACT
POST ACTH CONTROL

FIG 3

13

Adrenal Function and Steroid Excretion in Neoplastic Disease

*K Dobriner S Lieberman H Wilson, B Ekman O Pearson and L Eliel**

SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH NEW YORK CITY

In patients with neoplastic disease the excretion of adrenal cortical and gonadal steroid metabolites is markedly diminished and often certain steroids are no longer demonstrable (Fig 1) If one as

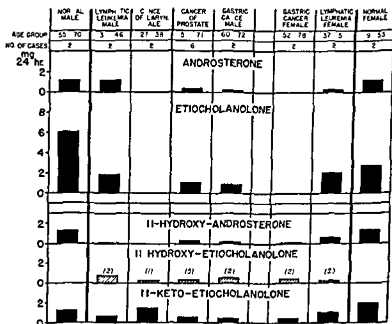


FIG 1

This investigation was aided by grants from the American Cancer Society (on recommendation of the Committee on Growth of the National Research Council) Ayerst McKenna and Harrison Ltd the Jane Coffin Childs Memorial Fund for Medical Research the Commonwealth Fund the Anna Fuller Fund the Lillia Babbitt Hyde Foundation the Albert and Mary Lasker Foundation and the National Cancer Institute of the National Institutes of Health U S Public Health Service

The question may then be asked whether stimulation of the adrenal by ACTH would restore the gland to a more nearly normal function If this were possible would the change in the adrenal secretion be reflected in an alteration in the course of the disease? There is evidence from the work of Heilman and Kendall that an adrenal hormone profoundly affects tumor growth in mice Furthermore Dougherty and White have shown that adrenal hormones are extremely active agents in the dissolution of lymphatic tissue

In order to study these questions in man we administered ACTH to a group of patients with cancer and lymphatic disease This is a cooperative study with Drs Pearson Eliel Rawson and Rhoads and the clinical findings will be reported separately I shall report the effect of ACTH on hormone production as evidenced by the steroid

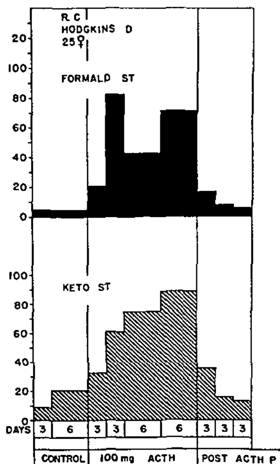


FIG 5

sumes that the steroid excretion is a measure of hormone production by the gland then one is forced to the conclusion that there is adrenal and gonadal dysfunction in malignancy Confirmation of altered adrenal function in neoplasia is afforded by the fact that 11 hydroxy etiocholanolone a compound of adrenal cortical origin, is found in the urine of a significant number of cancer patients whereas it is only

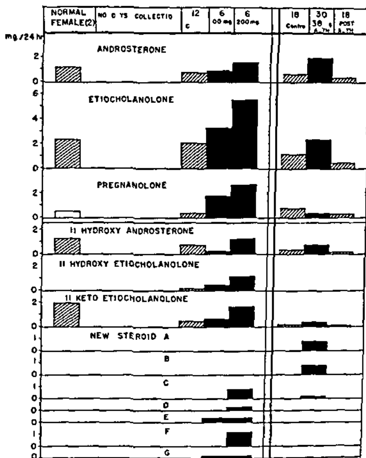


Fig 4

rarely present in the urine of normal individuals *Adrenal dysfunction* existed in 2 patients several years before there was any obvious manifestation of the tumor because 11 hydroxy etiocholanolone was consistently present before the tumor was discernible In one of these patients the excretion of this abnormal metabolite has continued for more than 5 years after surgical removal of the breast without recurrence of the lesion This indicates that adrenal function may be involved in the course or in the cause of neoplastic disease

where the formaldehydogenic steroids were determined Thru the cooperation of Dr Fuller Albright, we were also able to study the urinary steroid excretion of a breast cancer patient before, during and after administration of ACTH (Fig 3) Again a slightly increased steroid excretion was seen during the period of ACTH administration

The effect of ACTH is more clearly apparent when individual ster

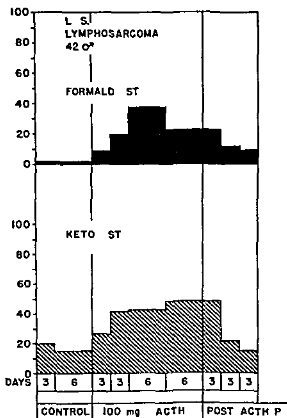


Fig 7

oids are examined Figure 4 shows the steroid excretion pattern of the 5 most abundant a ketosteroids in the same two subjects comparison is made with the pattern of 2 normal females of similar age The excre tion of these 5 substances during the control period in the cancer pa tients was somewhat less than that of normal subjects The effect of ACTH was slight but there is an indication that these 5 compounds were increased to a level very similar to that of the normal controls The pattern of the patient who received 200 mgs ACTH shows values somewhat above the normal range

metabolites in the urine Fig 2 illustrates the steroid excretion before during and after administration of ACTH in a female patient with cancer of the breast The values shown were obtained from the crude neutral extracts before fractionation by methods which have been described in detail elsewhere It is apparent that in this subject the administration of ACTH in dosage of 100 mg per day for 18 days resulted in only minor changes in the excretion of ketosteroid and reducing steroids Following a 12 day control period 100 mg of ACTH

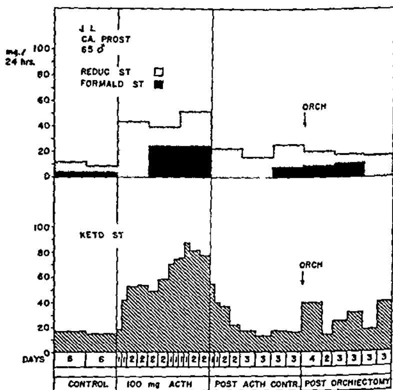


Fig 6

per day was again given for 6 days without any marked alteration of the urinary steroids When however 200 mg ACTH per day was given for a 6 day period there was a pronounced increase in steroid excretion measured by the Zimmermann reaction by the total reduction and by the production of formaldehyde after periodate oxidation Following cessation of ACTH the steroid excretion returned slowly to the control level It is possible even with these very crude measurements to demonstrate that there was a marked change in steroid excretion when adequate amounts of ACTH were administered Steroid excretion patterns were made during the intervals shown in Fig 2

that of a normal person Final evaluation must be postponed until it is possible to study the effect of ACTH administration on the urinary steroid excretion of normal subjects

In general the effect of ACTH measured by steroid excretion parallels the metabolic activity measured by nitrogen and electrolyte excretion In those instances where ACTH failed to elicit a marked

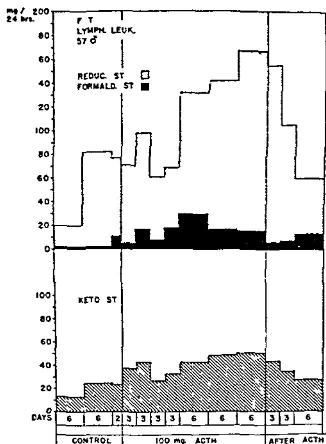


FIG 9

increase of steroid excretion there was a relatively small metabolic response On the other hand where ACTH provoked a pronounced effect on the steroid excretion there was similarly a very striking change in the excretion of nitrogen and electrolytes In Figs 5 through 10 it is possible to see the type of ACTH response observed in several patients with various dosage and time of administration There appears to be great individual variation when 100 mg of ACTH was given some subjects showing practically no change (Figs 2 and 10)

11 Hydroxy etiocholanolone was present in the urine of one of these two subjects and continued to be excreted at a markedly elevated level during stimulation of the adrenal gland by ACTH In the patient where 11 hydroxy etiocholanolone was absent during the control period ACTH did not cause the appearance of this compound in the urine This is a very striking result since it may be interpreted as indicating a specific adrenal disturbance In addition to the changes discussed it can be seen from Fig 4 that both patients excreted a series of new substances in appreciable amount under the influence of ACTH Some of these compounds whose structure is thus far unknown have been recognized previously in the urine of patients with Cushing s syndrome Here again is evidence that while ACTH has increased the steroid excretion it has not restored adrenal function to

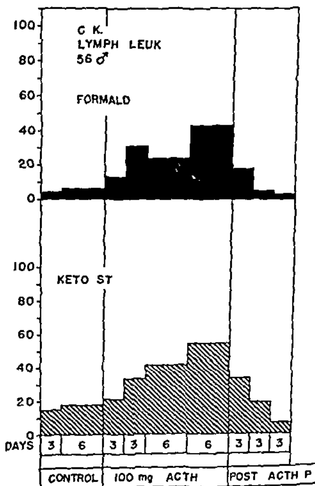


Fig 8

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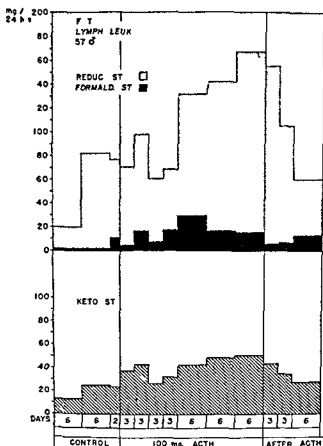


FIG 9

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whereas in other instances a very pronounced response was elicited (Figs 5 and 6)

DISCUSSION

DR LAURANCE W KINSELL I would like to ask Dr Dobriner whether there is a possibility that different preparations different batches of

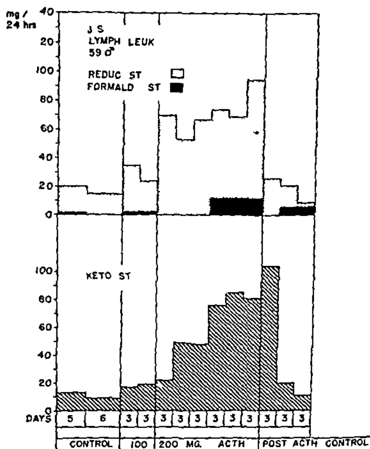


Fig 10

adrenocorticotrophin might account for these differences in responses in any of these individuals

DR K DOBRINER There is no indication We have had quite a number of lots and if we got a response we got it very quickly or as you saw the responses comparatively slowly in this type of patient

DR L L ENGEL (Huntington Memorial Laboratories, Massachusetts General Hospital Boston) I would like to show these data which in

dicate that still another class of steroid compounds namely, the neutral non ketonic alcohols can also reflect changes of the activity of the adrenal cortex

In this experiment (Fig 11), 11 dehydro 17 hydroxycorticosterone acetate was administered at a dosage of 100 mg per day for 5 days to a patient with Addison s disease * During this period the excretion of ketosteroids rose significantly but even more striking was the increase *in excretion of steroid alcohols measured colorimetrically as the hemi* dinitrophthalates It is also interesting that the pre treatment excretion of non ketonic alcohols in this patient was about one fifth of that found in normal subjects

This method provides another tool for the measurement of adrenal cortical function and should yield useful data in determining the effect of ACTH on the mobilization of steroids of the adrenal cortex

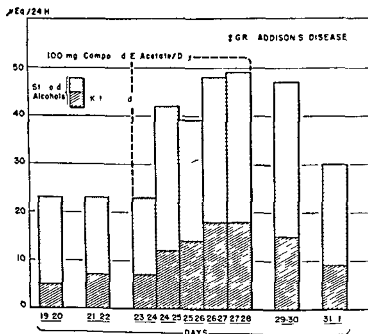


FIG 11 (From Engel L L Recent Progress in Hormone Research Vol 5 Laurentian Hormone Conference Proceedings New York Academic Press 1950)

* We a e indebted to Dr George Tho n of the Peter Bent Brigham Hospital for the specimens f om th s pat ent

14

Urinary Excretion of Steroids During Administration of ACTH

Harold L Mason

MAYO CLINIC ROCHESTER MINN

The urinary excretions of 17 ketosteroids and corticosteroids (essentially the same fraction as those designated as reducing steroids and ' 11 oxysteroids) were studied in 5 cases of rheumatoid arthritis in which ACTH (Armour) was administered In 3 cases the patients were women 49 45 and 40 years of age respectively (Tables 1 2 and 3) and in the fourth case the patient was a man 23 years of age (Table 4) The daily dosages are given in the tables in terms of the Armour standard In the fifth case (Table 5) the patient was a man 38 years of age who received varied doses of ACTH during an 87 day period

It will be noted that with respect to the urinary excretion of steroids, the response to 100–105 mg equivalent of the Armour standard varied greatly among the group of 3 patients who received ACTH at this level The maximal amounts of 17 ketosteroids and corticosteroid varied from approximately 23 mg to 45 mg and from 7 0 to 17 5 mg, respectively At this dosage level an increase in the urinary steroids was observed on the first and second day After stopping the administration of ACTH the amounts of corticosteroids fell rapidly to values within the range of normal values and in 1 case (Table 3) the amount of 17 ketosteroids fell to a level somewhat below that observed before treatment with ACTH was begun

In the case of the man who received 70 mg of ACTH daily (Table 4) the steroid excretions were less but they approached the amounts excreted by one of the women (Table 3)

In the case of the man who received varied amounts of ACTH (Armour) (Table 5) the first definite increase in corticosteroids was found on the third day and the first definite increase in 17 ketosteroids on the fourth day of the period during which he received 70 mg of ACTH During the next 6 days the corticosteroids increased slightly but the average 17 ketosteroid level was probably not significantly

Table 1

CORTICOSTEROID AND 17 KETOSTEROID EXCRETIONS DURING TREATMENT WITH ACTH (100 MG DAILY)

Date 1949	*Day of Period*	*Corticosteroids mg/24 hrs*	*17 Ketosteroids mg/24 hrs*
Control Period			
2/20–21		0.90	4.0
2/21–22		0.88	4.8
2/22–23		0.96	4.3
ACTH Period			
2/23–24	1	0.88	3.0
2/24–25	2	5.55	8.9
2/26–27	4	7.65	16.4
2/27–28	5	11.30	22.6
3/1–2	7	11.80	29.2
3/3–4	9	17.40	34.7
3/5–6	11	14.50	44.7
3/6–7	12	17.50	43.8
After Period			
3/7–8	1	3.58	22.0
3/8–9	2	2.86	9.4
3/9–10	3	1.12	4.9
3/10–11	4	0.50	5.6
3/11–12	5	0.54	5.6

greater than the one control value. A dose of 105 mg of ACTH did not increase the corticosteroids significantly or the average level of 17 ketosteroids. When the amount of ACTH administered was increased to 120 mg per day the amount of corticosteroids increased considerably but there was no significant change in the amount of

Table 2

CORTICOSTEROID AND 17 KETOSTEROID EXCRETIONS DURING TREATMENT WITH ACTH (100 MG DAILY)

Date 1949	*Day of Period*	*Corticosteroids mg 24 hrs*	*17 Ketosteroids m /24 hrs*
2/5–6	Control	0 51	3 5
2/6–7		0 51	3 6
2/7–8		0 58	1 8
		ACTH Period	
2/8–9	1	1 46	5 4
2/9–10	2	1 18	7 4
2/11–12	4	3 80	7 4
2/12–13	5	9 41	14 5
2/14–15	7	9 90	20 8
2/16–17	9		23 8
2/18–19	11	12 20	29 8
2/19–20	12	12 10	29 6
		After Period	
2/20–21	1	2 18	11 7
2/21–22	2	0 89	6 8
2/22–23	3	1 06	3 5
2/23–24	4	1 03	4 7
2/24–25	5	0 78	3 4
3/15–16	24	0 79	2 8

17 ketosteroids However during the prolonged treatment with 100 mg of ACTH (Armour) the excretion of both types of steroids varied a great deal from day to day and were considerably less than the amounts excreted by the other patients

In the first 4 cases 17 hydroxycorticosterone was isolated from the

Table 3

CORTICOSTEROID AND 17 KETOSTEROID EXCRETIONS DURING TREATMENT WITH ACTH (105 MG DAILY)

Date 1949	*Day of Period*	*Corticosteroids mg/24 hrs*	*17 Ketosteroids mg/24 hrs*
4/3–4	Control	0 64	5 4
4/4–5		0 40	7 0
4/11–12		0 75	7 4
	ACTH Period		
4/12–13	1	1 03	7 9
4/13–14	2	2 00	10 5
4/15–16	4	3 34	17 5
4/16–17	5	2 46	14 2
4/17–18	6	3 56	14 3
4/18–19	7	4 57	18 6
4/19–20	8	4 15	17 9
4/20–21	9	4 30	13 7
4/21–22	10	5 14	20 2
4/22–23	11	7 00	23 1
4/23–24	12	6 30	21 4
	After Period		
4/24–25	1	1 15	11 2
4/25–26	2	0 46	5 9
4/26–27	3	0 42	4 8
4/27–28	4	0 60	4 0
5/1–2	8	1 00	2 8
5/12–13	19	0 73	4 7
5/16–17	23	0 73	4 1
5/23–24	30	0 76	6 4

Table 4

CORTICOSTEROID AND 17 KETOSTEROID EXCRETIONS DURING TREATMENT WITH ACTH (70 MG DAILY)

Date 1949	*Day of Period*	*Corticosteroids mg /24 hrs*	*17 Ketosteroids mg /24 hrs*
4 22–23	Control	0 73	8 8
4/23–24		0 85	11 7
	ACTH Period		
4/25–26	2	2 28	17 0
4/26–27	3	4 58	18 6
4 27–28	4	4 83	19 9
4/28–29	5	5 42	17 5
4/29–30	6	4 74	16 3
4 30–5 1	7	3 83	11 4
5/1–2	8	5 70	18 4
5/2–3	9	4 32	21 1
5/3–4	10	4 53	15 8
5/4–5	11		18 7
	After Period		
5/5–6	1	5 52	17 4
5/6–7	2	1 59	6 7
5/7–8	3	0 44	8 2
5/8 9	4	0 48	10 5
5/11–12	6	0 54	6 3

urine collected during the treatment with ACTH Approximately 30 to 50% of the corticosteroids as determined chemically were isolated It was not possible to detect the presence of 17 hydroxy 11 dehydrocorticosterone (Compound E or Cortisone) although it may have been present in small amounts It appears from these results that

Table 5

Corticosteroid and 17 Ketosteroid Excretions During Treatment with ACTH

Date 1949	Day of Period	ACTH mg/day	Corticosteroids mg/24 hrs	17 Ketosteroids mg/24 hrs
5/20–21	Control	None	0.81	8.4
5/21–22	1	70	0.86	9.9
5/22–23	2		1.30	10.3
5/23–24	3		1.29	14.9
5/24–25	4		1.57	11.2
5/25–26	5		1.77	11.6
5/27–28	7		1.57	12.7
5/28–29	8		1.65	10.8
5/29–30	9	105	1.52	7.0
5/30–31	10		1.74	8.6
5/31–6/1	11		1.44	10.1
6/1–2	12	140	2.46	13.0
6/4–5	15	125		
6/5–6	16	120	1.36	14.2
6/7–8	18		2.53	10.5
6/9–10	20		2.77	11.5
6/13–14	24		2.75	11.3
6/15–16	26		5.32	11.7
6/17–18	28	75	2.51	8.1
6/19–20	30		1.66	10.4
6/21–22	32	90	1.50	14.1
6/23–24	34		1.26	10.1
6/26–27	37		2.88	15.3

Table 5 (continued)

CORTICOSTEROID AND 17 KETOSTEROID EXCRETIONS DURING TREATMENT WITH ACTH

Date 1949	*Day of Period*	*ACTH mg/day*	*Corticosteroids mg/24 hrs*	*17 Ketosteroids mg/24 hrs*
6/28–29	39	90	1.61	16.5
6/30–7/1	41	100	1.89	12.0
7/4–5	45		2.22	14.2
7/6–7	47		1.90	17.6
7/8–9	49		1.81	16.4
7/10–11	51		2.88	18.5
7/12–13	53		1.74	22.2
7/14–15	55		2.04	8.1
7/17–18	58		3.01	18.3
7/19–20	60		2.54	19.8
7/21–22	62		1.89	9.6
7/24–25	65		2.40	17.8
7/26–27	67		2.94	19.9
7/28–29	69		3.18	9.9
7/31–8/1	72		2.03	9.4
8/3–4	75		2.20	15.0
8/7–8	79		3.14	20.2
8/10–11	82		1.62	10.6
8/14–15	86		1.60	14.5
8/15–16	87			
8/16–17	88	None	0.43	6.8
8/17–18	89		0.45	3.1
8/21–22	93		0.74	4.6
8/28–29	100		0.58	5.0

stimulation of the human adrenal cortex with ACTH promotes the secretion of 17 hydroxy corticosterone rather than the secretion of Compound E

DISCUSSION

DR WILLIAM H DAUGHADAY I would like to ask Dr Mason how he explains the difference in corticoid excretion with ACTH as compared to Compound E administration

With ACTH the elevation of urinary corticoids is usually large while it may be quite small following Compound E administration Is this due to the fact that enough Compound E has not been given or that the natural adrenal hormones appear in the urine to a greater extent?

DR HAROLD L MASON I think we would have to know more about the metabolism of Compound F which apparently is produced in large amounts by the adrenal stimulated with ACTH Possibly we would obtain in the urine a greater return of corticosteroids with Compound F, although with one experiment, we did not

Another thing is that Compound E is given in one or two injections whereas presumably the adrenal is producing these steroids continuously which may have considerable effect on the amount excreted

DR ALLAN KENYON Perhaps you just answered this but I want to ask whether you have any idea of the amounts of Compound F required to give the amounts of urinary material that are secured by use of the adrenocorticotrophic hormone

DR HAROLD L MASON We haven t that information but the indications are that it would be considerably more than 100 mg per day probably several hundred mgs

DR ALBERT DORFMAN I assume Dr Mason that you have not been able to detect 17 hydroxy corticosterone after Compound E administration?

DR HAROLD L MASON Only by means of a color reaction I have isolated Compound E after administration of Compound E and the isolated material gives the color reaction with concentrated sulfuric acid which is characteristic of an 11 hydroxy adrenal hormone but I haven t been able to separate any Compound F from this material The color reaction is only an indication

DR GREGORY PINCUS I would like to second this idea about 11 hydroxy compounds because in the work we have been doing with perfusing adrenal glands with possible precursors of these substances we get only 11 hydroxylated compounds, and have been unable to isolate any 11 ketosteroid compounds

DR WILLIAM Q WOLFSON In a patient with rheumatoid arthritis receiving Cortisone under the direction of the Michael Reese Rheumatoid Arthritis Research Group the urinary ketonic corticoids were studied by the technique of paper chromatography The urine extracts were prepared by the method of Heard and Sobel The Girard T hydrazones were synthesized at 45°C by the technique of Zaffaroni Burton and Keutmann applied to paper sheets in the usual manner and the chromatograms developed with a fast tert butanol sec butanol mixture saturated with water After the sheets were dried the spots were localized with the iodoplatinate reagent as described by Zaffaroni and his associates

During Compound E administration the chromatogram showed only one band This band had an Rf slightly slower than the Girard T reagent itself and since it corresponded in position with the band given by pure samples of Compound E or F it was designated EF The position of the EF band on the chromatogram corresponds to that for a 3 20 di ketone with additional slowing due to hydroxyl groups or to ketone groups which do not form a Girard T hydrazone (e g the 11 ketone group) Presumably from the study of Dr Mason the EF band noted after Cortisone administration was largely due to Compound E

When Compound E was withdrawn 2 new bands designated *X* and *Y* appeared and were present for 6 days following hormone withdrawal Both were considerably weaker than the EF band previously had been and both moved with an Rf considerably slower than the EF band *X* the faster of the two predominated in the pooled urine collected during the first 3 days after Cortisone withdrawal

DR GEORGE W THORN It might be helpful to recall that on our assay curves 4 mgs of ACTH give the same fall in eosinophils as the single injection of 12 mgs of Compound F or 25 mgs of Compound E

DR HAROLD L MASON Do you find Compound F is more effective than Compound E with respect to eosinophils?

DR GEORGE W THORN That is right

DR LAURANCE W KINSELL In normal individuals?

DR GEORGE W THORN In Addisonians

15

ACTH and Gastrointestinal Enzymes

*Seymour J Gray Howard M Spiro and Robert W Reifenstein**

PETER BENT BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

In studying the interrelationship of gastrointestinal enzymes in response to different types of stimulation we became interested in ACTH, particularly as it relates to the effect of stress upon the gastro intestinal tract

There is good evidence that the peptic glands of the stomach have an endocrine as well as an exocrine function similar to that of the pancreatic acini which secrete amylase and lipase into the pancreatic ducts as well as into the blood stream [1]

The peptic glands of the gastric mucosa secrete a pro enzyme or precursor pepsinogen directly into the blood stream [3] Pepsinogen is transported to the kidneys and is excreted into the urine as uropepsin [1]

Uropepsin is a proteolytic enzyme normally present in human urine which may well be derived from the secretion of pepsinogen directly into the blood stream by the secreting peptic cells Its measurement in the urine reflects the peptic activity of the stomach That uropepsin originates in the stomach exclusively is demonstrated by the fact that it disappears from the urine of gastrectomized animals and is absent from the urine of patients with pernicious anemia

The peptic glands excrete pepsinogen into the lumen of the stomach where it is converted to active pepsin in the presence of hydrochloric acid Pepsin given orally or intravenously does not alter uro pep in excretion [1]

The probable identity of uropepsin with the internal secretion of pepsinogen is supported by the fact that the intravenous injection of pepsinogen results in a considerable increase in uropepsin excretion but the oral administration has no effect [1]

The purpose of this presentation is to report the effect of ACTH upon uropepsin excretion

* We wish to acknowledge the cooperation and interest during the course of these studies of Drs George W Thorn and Peter Forsham of the Peter Bent Brigham Hospital and Drs Theodore Bayles and Carlyle Stout of the Robert Breck Brigham Hospital

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The increase in the 24 hour excretion of uropepsin after ACTH administration is not related to an increased urine volume (Fig 3) The 24 hour excretion of uropepsin increased from the normal of 1800 units to 4300 units upon the administration of 40 mgm ACTH and gradually increased to 5300 units after 5 days of ACTH administration The urine volume did not vary appreciably during this period while the uropepsin excretion calculated on the basis of units per cubic centimeter of urine paralleled the increase in the 24 hour uropepsin excretion This increase was observed particularly on Day 7 when the total 24 hour urine volume fell while the units of uropepsin

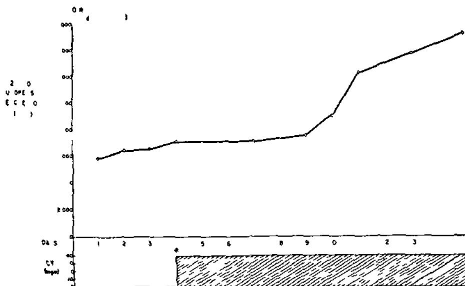


Fig 2 Effect of ACTH upon uropepsin excretion

excreted per cubic centimeter of urine increased sufficiently to produce an increase in the 24 hour excretion

Patients with gastric cancer usually excrete very little or no uropepsin (Fig 4) The administration of 2 mgm of epinephrine intravenously increased the uropepsin excretion to 1000 units within 24 hours The level promptly fell to 0 when the epinephrine was discontinued Three days later 50 mgm of ACTH produced a similar prompt increase in uropepsin excretion to 1000 units The urine again contained no uropepsin the day after ACTH was discontinued

That the peptic gland of the gastric mucosa is indispensable for the production of uropepsin is demonstrated by the fall in uropepsin from 2400 units to 0 after total gastric resection (Fig 5) ACTH did not increase the uropepsin excretion after total gastric resection

The gastric mucosa of patients with pernicious anemia (Fig 6)

RESULTS

ACTH produces a marked increase in uropepsin excretion (Fig 1) Uropepsin was measured by a modification of Mirsky s method based upon the Folin Ciocalteu procedure [1,4] The administration of 50 mgm of ACTH daily for 2 days caused an immediate increase in the 24 hour urinary excretion of uropepsin from 0 units to 4300 units When the ACTH was discontinued, the urinary uropepsin excretion fell to 0 ACTH re administered 4 days later again caused an immediate increase in uropepsin excretion When the dose was diminished on suc

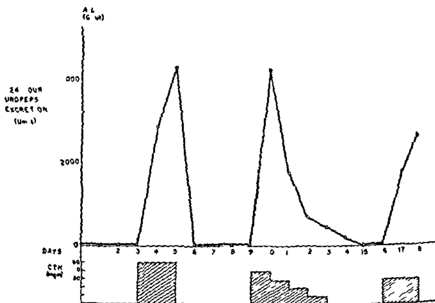


Fig 1 Effect of ACTH upon uropepsin excretion

cessive days from 40 mgm to 30, 20 and 10 mgm the uropepsin output fell accordingly from 4100 units to 1800 700 and 400 units respectively Upon the discontinuation of ACTH the uropepsin level again fell to 0 and responded a third time to ACTH stimulation 3 days later

Patients with an active duodenal ulcer excrete an increased amount of uropepsin in the urine (Fig 2) as evidenced in this case by a level of 6000 units prior to ACTH administration compared to the normal of 2000 The respon e to ACTH was delayed for 5 days, presumably because of the very high initial uropepsin level After 11 days of ACTH administration, the uropepsin excretion increased to the unprecedented level of 16 000 units This exceedingly high level has not been observed previously and occurs only after ACTH stimulation

FIG 5 Effect of ACTH upon uropepsin excretion

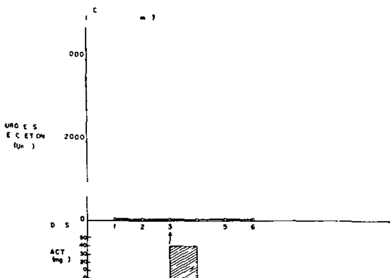


FIG 6 Effect of ACTH upon uropepsin excretion

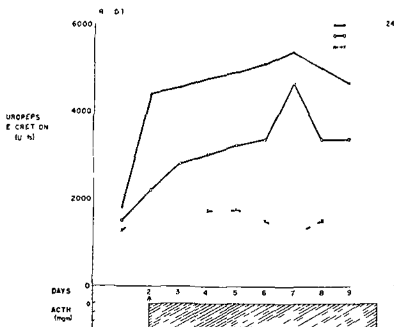


Fig 3 Effect of ACTH upon uropepsin excretion

4000

24 HOUR
UROPEPSIN
EXCRETION

2000

0

DAYS 1 2 3 4 5 6 7 8 9 10 11 12

Fig 4 Effect of epinephrine and ACTH upon uropepsin excretion

3000
24 HOUR UROPEPSIN EXCRETION (units)
2000
1000
0
DAYS 1 2 21 22 23 24 25
ACTH (mgm) 30 20 10 0

FIG 5 Effect of ACTH upon uropepsin excretion

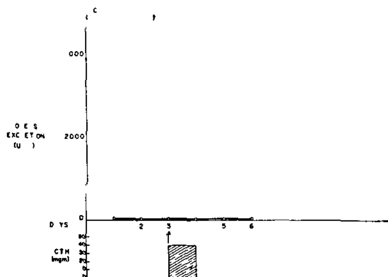


FIG 6 Effect of ACTH upon uropepsin excretion

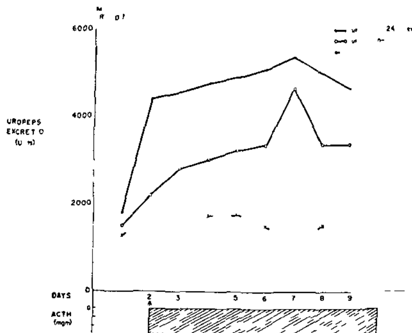


FIG 3 Effect of ACTH upon uropepsin excretion

4000
24 HOUR
UROPEPSIN
EXCRETION
2000
0
DAYS
1
2
3
4
5
6
7
8
9
10
11
12

FIG 4 Effect of epinephrine and ACTH upon uropepsin excretion

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DISCUSSION

VOICE We would be very interested to know what happened to the ulcer in the patient with peptic ulcer

DR SEYMOUR J GRAY The patients we have studied have not been maintained on ACTH for a long enough period of time to evaluate its effect on peptic ulcer Most of the experiments have been of short duration because of our limited supply of ACTH We have been studying the effect of ACTH upon gastric secretion particularly in reference to changes in mucin pepsin lysozyme and acid

undergoes diffuse atrophy involving the peptic glands as well as the acid forming glands Pepsinogen and consequently pepsin and uropepsin are absent ACTH in these patients produced no increase in uropepsin excretion

DISCUSSION

ACTH produces a marked increase in uropepsin excretion The intact gastric mucosa is essential for this response ACTH failed to increase uropepsin excretion after a total gastrectomy and in pernicious anemia with diffuse gastric atrophy Whether ACTH acts directly upon the gastric mucosa or is mediated through the adrenal gland awaits further study on the Addisonian patient

The evidence at present indicates that ACTH stimulates the peptic gland to secrete pepsinogen into the blood stream producing an increase in uropepsin excretion That it stimulates the exocrine function of the gland as well as the endocrine is revealed by the increase of pepsin in the gastric juice after prolonged ACTH administration

The increased excretion of uropepsin after ACTH in all probability is not the result of alteration of the renal threshold In the presence of a high uropepsin level of 6000 units and presumably a high blood pepsinogen level (see Fig 2) the administration of ACTH for 5 days was required before an effect was noted The uropepsin excretion then gradually increased over a period of 4 days This suggests stimulation rather than altered renal threshold The increase in gastric juice pepsin after ACTH administration also suggests that the peptic gland is being stimulated to produce pepsinogen and that both the exocrine and endocrine functions are being affected

Preliminary investigations of the effects of ACTH administration upon patients with chronic ulcerative colitis indicate that other gastrointestinal enzymes such as lysozyme may be altered What effect enzyme changes may have upon the course of disease processes remains to be determined

CONCLUSIONS

1 ACTH increases the excretion of uropepsin in the urine

2 The effect of ACTH upon uropepsin excretion is abolished by total gastric resection

3 ACTH does not stimulate uropepsin excretion in pernicious anemia

4 Evidence is presented which indicates that ACTH stimulates the endocrine and exocrine functions of the peptic gland

same clinical disturbance there was also an increase in the excretion of 17 ketosteroids and 11 oxysteroids with a slight increase in the excretion of sodium and potassium

The 2 infants who had marked Addisonian like symptoms were maintained on 3 mg desoxycorticosterone (Asquith) and 75 mg desoxycorticosterone (Boyle) In both of these cases ACTH caused a small sodium loss but had little effect on the potassium excretion One of these patients (Asquith) showed a marked rise in the excretion of

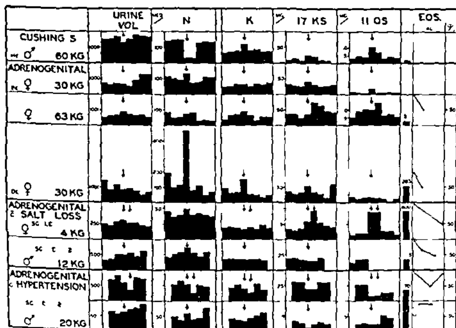


Fig 1

17 ketosteroids and 11 oxysteroids and the administration of ACTH produced a clinical relapse with dehydration and weight loss

The infant with macrogenitosomia praecox and abnormal adrenal glands had a hypertension of 150 90 which was not reduced by benzodioxane Although the serum electrolytes were normal it was thought that the hypertension was probably the result of the adrenal disorder ACTH (Armour) was given on 2 occasions and in neither instance was there a rise in 17 ketosteroids or 11 oxysteroids in fact the steroid excretion appeared to fall with the injection of ACTH A normal fall in the level of circulating eosinophils was not produced and the changes in sodium and potassium excretion were not consistent

16

The Response to ACTH in Various Types of Adrenal Hyperplasia

Lawson Wilkins Robert Klein and Roger A Lewis

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE AND THE HARRIET LANE HOME OF THE JOHNS HOPKINS HOSPITAL BALTIMORE

We have used ACTH (Armour) to study the activity of the adrenals in a number of different types of hyperplasia (Fig 1) Studies were made on 1 patient with Cushing's syndrome (while he was re ceiving methyl testosterone and the disease was partially arrested), on 3 females with congenital adrenal hyperplasia with pseudohermaph roditism, on 2 young infants (1 male and 1 female) having the adreno-genital syndrome accompanied by a marked tendency to salt loss (which was being controlled with desoxycorticosterone), and in 1 male with macrogenitosomia praecox who had marked hypertension and very large adrenal glands

During the studies the patients were maintained on diets constant with respect to calories nitrogen sodium and potassium ACTH (Armour) was given at 4–6 hour intervals for 24–48 hours The total dose amounted to 1–3 mg kg body weight The most significant changes which were noted occurred in the excretion of water sodium potassium, 17 ketosteroids and 11 oxysteroids The urinary findings during a 3 dav control period before the day of treatment with ACTH and the 4 subsequent days are shown in the illustration The level of circulating eosinophils and the percentage fall in 4–24 hours are also indicated in the illustration

The patient with Cushing s syndrome responded in the same fash ion that normal individuals have been reported to react There was an increase in the output of 17 ketosteroids and 11 oxysteroids with a marked retention of sodium and an increased excretion of potassium

Of the 3 patients with adrenogenital syndrome who had no dis turbance in electrolyte metabolism and no hypertension one (Dent) showed a marked loss of sodium Although high at the start the excre tion of 17 ketosteroids was increased In the other 2 patients with the

same clinical disturbance there was also an increase in the excretion of 17 ketosteroids and 11 oxysteroids with a slight increase in the excretion of sodium and potassium

The 2 infants who had marked Addisonian like symptoms were maintained on 3 mg desoxycorticosterone (Aisquith) and 75 mg desoxycorticosterone (Boyle) In both of these cases ACTH caused a small sodium loss but had little effect on the potassium excretion One of these patients (Aisquith) showed a marked rise in the excretion of

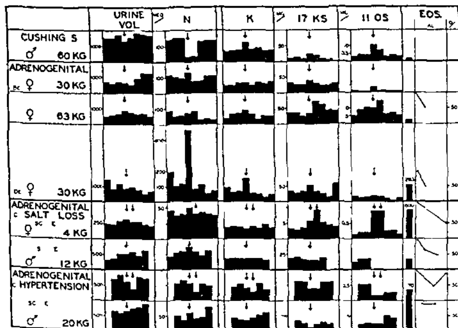


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The infant with macrogenitosomia praecox and abnormal adrenal glands had a hypertension of 150/90 which was not reduced by benzodioxane Although the serum electrolytes were normal it was thought that the hypertension was probably the result of the adrenal disorder ACTH (Armour) was given on 2 occasions and in neither instance was there a rise in 17 ketosteroids or 11 oxysteroids in fact the steroid excretion appeared to fall with the injection of ACTH A normal fall in the level of circulating eosinophils was not produced and the changes in sodium and potassium excretion were not consistent

SUMMARY

1 The administration of ACTH (Armour) in Cushing's syndrome produces the same effect as in normals with increased steroid excretion and sodium retention

2 The administration of ACTH (Armour) in cases of adrenal hyperplasia with virilism or precocity causes no increase in sodium retention and may cause a moderate to marked increase in sodium excretion despite the increase in steroid excretion which usually occurs

3 It is suggested that the Addisonian symptoms which may occur in cases of adrenogenital syndrome may be due in part to the increased production of adrenal hormones which produce salt loss (such as Compound E) as well as decreased production of salt retaining hormones (such as desoxycorticosterone)

DISCUSSION

DR LOUIS J SOFFER (Mount Sinai Hospital New York) As one of the features in which the patient with virilism behaves differently following the administration of ACTH as contrasted with patients with Cushing s syndrome may I show two slides please

Fig 2 shows a patient with Cushing s syndrome who has bilateral adrenocortical hyperplasia This patient was placed on a careful balance study The outstanding feature was the marked difference in the calcium excretion of this patient in contrast to the patient with the virilizing manifestations

The patient with Cushing s syndrome went into negative calcium balance and, as described earlier by Dr Kinsell, the major degree of excretion of calcium occurred in the stool rather than in the urine

DR LAURANCE W KINSELL Was there an increase in stool phosphorus too?

DR LOUIS J SOFFER Yes In addition we also did nitrogen balance studies and there was an increase in the urinary excretion of nitrogen

Fig 3 shows a patient who had marked evidence of virilism, and with the administration of 100 mgs of ACTH a day around the clock over a 4 day period she behaved quite differently from the patient with Cushing s syndrome In the former there occurred no increase in the urinary excretion of calcium and no increase in the stool excretion of calcium This patient stayed in constant calcium balance

From the clinical point of view I think this observation is significant in that osteoporosis is never observed in the patient with virilism

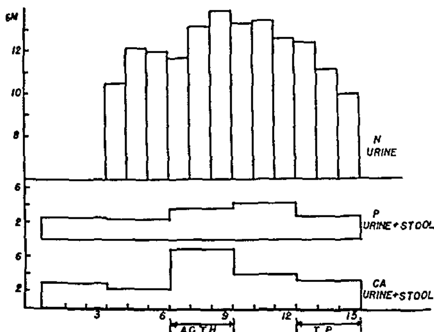


Fig 2

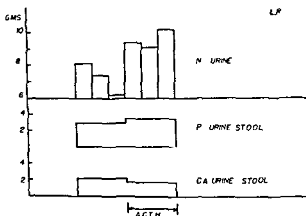


Fig 3

without Cushing's syndrome regardless of the kind of underlying pathology observed This is in contrast to the frequent presence of osteoporosis in patients with Cushing's syndrome The factors responsible for the osteoporosis in the latter group are at least two (1) A decrease in the protein matrix as suggested by Fuller Albright and (2) a decrease in available calcium for the laying down of bone The

Fig 4 Patient R H M G H #615754 *female* 50 with advanced carcinoma of breast Design of experiment sodium balance urinary chloride, theoretical weight curves, and serum Na and Cl during treatment with ACTH For other data on this study see Fig 5

latter lack is probably related to the constant excessive fecal loss of calcium

DR GEORGE W THORN I think we can say definitely that Compound E is a salt retaining hormone in the absence of any other adrenal hor mone in a patient In other words the untreated patient with Addi

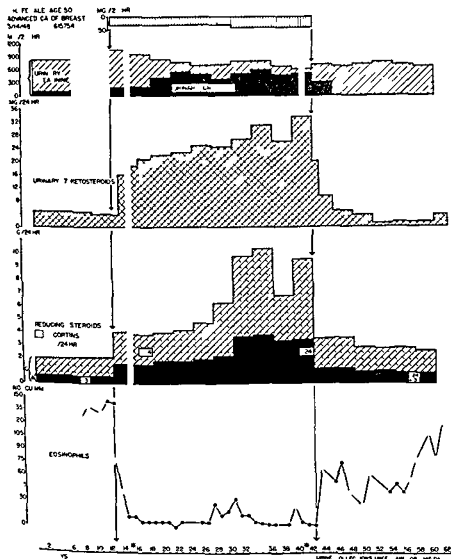


Fig 5 Same patient R H urinary creatinine creatine 17 ketosteroids reducing steroids (A = Aqueous fraction C = Crude fraction) biological cortin (M U = mouse units) and circulating eosinophils

son s disease retains sodium on Compound E This does not necessarily obtain in the presence of desoxycorticosterone therapy under which circumstance Compound E may induce sodium loss It is also evident that following the administration of ACTH in patients with intact adrenals one can make no prediction as to what will happen to the sodium and chloride balance One patient may experience sodium retention one patient may have little or no change, and another may actually have increased sodium excretion

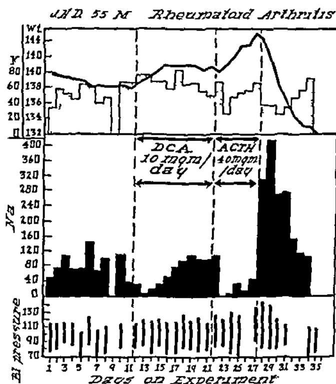


Fig 6

We have seen an edematous patient given ACTH experience diuresis with increased sodium excretion

DR FREDERIC C BARTTER I would like to add a note of caution in the interpretation of results which seem to show a paradoxical effect of a hormone when given together with another Fig 4 shows a part of a balance study in a patient with advanced carcinomatosis Thirty four mg of ACTH were given daily for 18 days then 43 mg daily for 12 days ACTH produced the expected sodium retention for 12 days then with absolutely no change in procedure there followed a pronounced sodium diuresis If a second hormone had been given on day

13 it would have appeared to have a paradoxical effect on sodium This same patient was treated some months later while on the same diet, with 100 mg of ACTH a day Interestingly enough she again went into spontaneous sodium diuresis on the thirteenth day

DR LAURANCE W KINSELL What was the ketosteroid excretion pattern in that patient do you recall roughly? You have two factors which affect sodium and potassium in somewhat different directions The

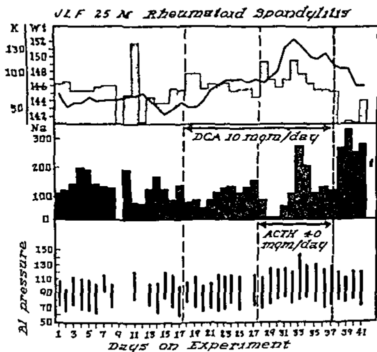


Fig 7

one acts upon the renal mechanism and the other acts upon the relative intracellular sodium and potassium

DR FREDERIC C BARTTER This is the same patient Dr Dobriner spoke of Fig 5 shows the results of 17 ketosteroid and reducing steroid assays during this study When the sodium diuresis was beginning (day 25) no change in steroid pattern was apparent With the higher dosage of ACTH the 17 ketosteroids rose slightly the reducing steroids markedly

DR FRANK H TYLER A patient with rheumatoid arthritis was treated with desoxycorticosterone and the same phenomena occurred An

initial positive sodium balance was established on desoxycorticosterone followed by an excretion above the level of the control period When the desoxycorticosterone was discontinued and ACTH instituted immediately, even more striking sodium retention occurred and persisted throughout the period it was given however that was only 6 days

Fig 6 shows that it was discontinued at this point because the patient developed massive peripheral edema Daily sodium excretion went as high as 411 milli equivalents per day after ACTH was stopped

In another patient the escape from positive sodium balance on DCA is also seen (Fig 7) When ACTH was added to the regime, he again retained sodium for a brief period and then escaped in spite of the simultaneous administration of DCA and ACTH

17

The Adrenal Thyroid Relationship*

R S Reiss D S Riggs George W Thorn and Peter H Forsham

PETER BENT BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

Our interest in adrenal thyroid relationships was stimulated by 2 incidental findings over the past 3 years during our work on ACTH and Cortisone

1 The often poor response in patients with hypothyroidism to the 4 hour and 48 hour ACTH tests[1] suggesting adrenal insufficiency in the absence of any clearcut clinical evidence for it

2 The finding of an initial increase in the rate of uptake of I 131 by the thyroid in patients with Addison s disease given Compound E acetate and the marked depression of the accumulation gradient of I 131 following therapy of more than 4 days duration [2]

From these preliminary observations it appeared that low thyroid function might slow down adrenal cortical activity whereas certain adrenal cortical hormones apparently depress thyroid function

A number of cases of hypothyroidism were given the 4 hour and 48 hour ACTH tests[1] when their BMR was of the order of minus 30% of normal *The majority but not all patients showed an Addisonian* response Examples are shown in Table 1 Some of these patients were given thyroid extract or intravenous thyroxine and following that therapy the adrenal cortical response to ACTH became normal, in most but not all instances

From these observations one might infer that rapid adrenal cortical activation by ACTH is dependent on adequate thyroid hormone as are most other tissues and such findings emphasize the extreme caution which should be exercised in giving cases of hypothyroidism suspected of adrenal cortical insufficiency therapeutic doses of thyroid without allowing sufficient time for the adrenal cortex to increase the rate of hormonal synthesis

In our studies on the effect of Compound E acetate in patients with Addison s disease[3] we made use of the method of Astwood and Stanley[4] to measure the rate of radioactive iodine (I 131) uptake over

*Part of this work was carried out with the aid of a grant from the United States Public Health Service which is gratefully acknowledged

the thyroid after giving 50 to 100 millicuries of I 131 by mouth in the fasting state In this method a straight line may be obtained by plotting counts per minute over the thyroid gland against the square root of the time elapsed since the administration of I-131 The slope of this line is known as the *accumulation gradient* ranging from 3 to 8 in our normal group whereas 30 different patients with Addison s disease showed a low average of 3 4 with a range from 0 7 to 9 0 The method of Winkler et al was used for protein bound iodine determination [5]

Compound E acetate in oil was administered intramuscularly every 6 hours to 5 patients with Addison s disease and one case of

Table 1

THE 4 HOUR ACTH TEST AT VARYING LEVELS OF BMR

Patient	*Sex*	*Age*	*BMR*	*Eos 0 Hr*	*Eos 4 Hr*	*% Change*	*BMR*	*Eos 0 Hr*	*Eos 4 Hr*	*% Change*
P W	I	46	−24	256	260	+11				
M R	F	49	−30	219	228	+4	+6	249	143	−43
F I	M	47	−30	237	181	−24				
C P	M	52	−36	169	128	−24	−14	162	37	−77
M O C	M	58	−31	153	91	−41				
V McD	M	49	−21	121	56	−54	+20	81	28	−66
NORMAL			0	186	25	−87				

THE 48 HOUR ACTH TEST AT VARYING LEVELS OF BMR

Patient	*BMR*	*Eos 0 Hr*	*Eos 48 Hr*	*17 Ketosteroids mg/24°* Control	24 Hr	48 Hr
M R (F)						
	−7	263	86	1 9	2 5	4 5
	+8	249	212	1 3	5 8	5 7
			? allergy			

panhypopituitarism whose response to Armour s thyrotropin (30 mg) showed that the thyroid was still capable of responding to pituitary stimulation (Fig 1) One notes a rise in the accumulation gradient on 50 mg or more of Compound E acetate per day for only 2 to 3 days Thereafter a decline in the gradient sets in Subcutaneous pellets of Compound E acetate releasing less than 5 mg per day proved quite active in suppressing the accumulation gradient over a matter of weeks and 5 months after implantation when these 50 mg pellets had been resorbed the gradient once again had returned to the control level Changes in gradient on therapy were much less marked in the case of panhypopituitarism

Upjohn's Lipoadrenal Cortex showed the same sequence of effects in a patient with Addison's disease (Fig 2) and the 3 day rise in gradient was obtained in 4 others in whom the extract was then discontinued

A patient with gout but otherwise normal given ACTH 10 mg q 6 h i m, responded well as shown by a fall in the eosinophils from 338 to 8 per cu mm in 5 days and a rise in 17 ketosteroids from 7 4 to 18 4 mg a day in 48 hours The already low gradient of 1 8 was decreased to a barely measurable one of 0 1 after 5 days of such therapy

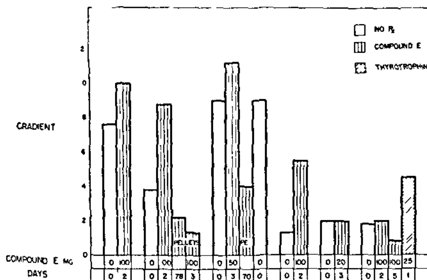


FIG 1 Effect of Compound E on I^{131} uptake in patients with Addison's disease and panhypopituitarism

With findings of this type we decided to investigate the effect of adrenal cortical stimulation on hyperthyroidism having Marine's work very much in our minds

Four patients with frank *hyperthyroidism* were treated with ACTH 2 showed marked improvement 1 little improvement and another no change at all The reasons for this variable response are not fully understood at this time The patient showing the greatest rise in 17 ketosteroid output also showed the best response and a poor rise was associated with the worst response The duration of the hyperthyroid state was shorter in the successfully treated patients

Before showing any clinical improvement all the patients went through a period of increased toxicity resembling a thyroid storm in miniature This began during the first day of treatment and extended

over a period of from 3 to 10 days after which gradual clinical improvement began in the successfully treated cases

In all four patients the I 131 accumulation gradient rose for 24 to 48 hours and then fell The maximal counts per minute over the thyroid however showed a much more marked decrease (Fig 3) the exact significance of which remains obscure The BMR decreased in 2 patients and failed to fall in another 2 In every instance the accumulation gradient fell long before there was any change in BMR and ir respectively of it

In the 2 successfully treated cases there was marked decrease in thyroid size and in one instance the gland removed at operation was smaller than normal In this patient a 33 year old female acute thyrotoxicosis had begun 2 months prior to treatment and was brought under control in 2 weeks on ACTH as shown in Table 2 The other

Table 2

EFFECT OF ACTH ON I 131 UPTAKE BMR AND PROTEIN BOUND IODINE IN A PATIENT WITH THYROTOXICOSIS (C O FEMALE 33 YEARS)

Day of Rx	*Eos No per cu mm*	*ACTH mg 24 h*	*17 Ks mg 24/h*	*Gradient I 131*	*BMR %*	*Protein Bound Iodine gamma %*
−2	144	0	9 1	45	+35	9 7
−1	)5	0		45	33	12 1
2	0	40	24 2			
3	0	40		45		
6	2	40		35	25	
8		40				6 2
10	30	40		25	12	5 6
11	13	80				
13		80	65)	18	13	6 0
14	0	80		17		5 0

Thyroidectomy on the 15th day showed a small thyroid (8 gm) with involution and reaccumulation of colloid and cuboidal follicular epithelium for the most part There were no lymphocytes seen

case H H, a 45 year old female, had shown symptoms of mild hyperthyroidism for 7 years with an acute exacerbation, 1 month prior to institution of ACTH therapy After a 5 day course of 10 mg of ACTH q 6 h i m, the accumulation gradient had fallen from 16 to 10 (Fig 3), the thyroid gland had gone down in size and the pressure symptoms no longer existed After stopping ACTH there was a symptomatological exacerbation which proved transitory and thereafter a spontaneous remission in the disease occurred so that 3 months later

the gradient was 7, there was a 7 pound weight gain and the size of the thyroid remained as it had been at the end of the 5 day course of ACTH

A case showing little clinical improvement was that of M R A, a 20 year old colored female in whom 17 days of ACTH given in amounts of up to 120 mg per day in the usual 4 dose fashion failed to depress the BMR, but did lead to a significant decrease in the size of the thyroid gland a fall in protein bound iodine from 14 to 7 4

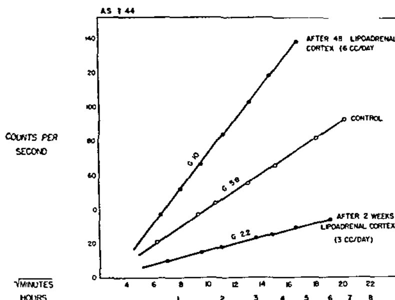


FIG 2 Effect of lipoadrenal cortex on I^{131} uptake in a patient with Addison s disease

gamma per 100 ml and in the gradient from 24 to 16 a value still above normal 17 Ketosteroid excretion never rose above 18 mg per day in contrast to 66 mg in C O who showed a satisfactory response

In A F a 52 year old female with a rather severe state of hyperthyroidism of at least 1 year s duration 10 days on 80 to 120 mg of ACTH failed to change the clinical state the BMR did not decrease and the 17 ketosteroids rose to only 21 mg per day although eosinophils went from 128 to 2 per cu mm

The effect of adrenal cortical stimulation on the hyperthyroid state appears variable Changes in protein bound iodine appear more marked than clinical improvement

On the assumption that the adrenal steroids might act on thyroid activity by suppressing TSH secretion by the anterior pituitary and

because of the possible relation of that to *exophthalmos* 2 patients with this affliction were investigated

Patient M C, a 45 year old female had developed exophthalmos following subtotal thyroidectomy on 2 occasions 2 millicuries of I 131, propylthiouracil and iodine treatment Exophthalmometric measurements showed a proptosis of 27 mm in the right eye and 22 mm in the left eye The patient was given ACTH in 4 equally divided daily doses beginning with 50 40 and 60 mg per day and then continuing

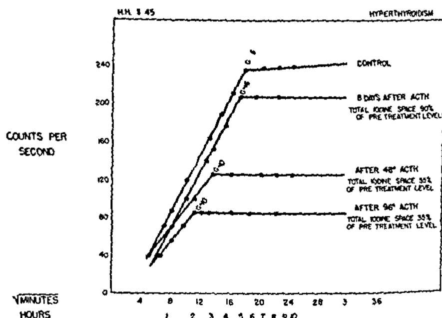


Fig 3 Changes in total I^{131} uptake after ACTH administration

on 80 mg a day for 5 days Coronary pain apparently related to the posterior pituitary contamination of the ACTH employed necessitated the early interruption of the treatment The patient was leveled off on 50 and 20 mg a day When treatment was stopped the exophthalmos had been reduced to 23 and 19 mm on the right and left eyes respectively Within a week the exophthalmos had reached the pre treatment state while the thyroid gland which had been reduced twofold in size to palpation was large again

Patient L C a 66 year old male developed malignant exophthalmos over a 3½ year period following subtotal thyroidectomy for well documented hyperthyroidism The exophthalmos was treated with thyroid extract and iodine and pituitary irradiation totalling 750 R in 3 separate courses all to no avail Treatment was discontinued for the last year and the patient was unable to close the injected eyes and

had to sit up at night Intramuscular injections of 20 mg of ACTH every 6 hours were given for 2 weeks and for another 6 days 20 mg every 8 hours A P measurements of the eyes in excess of 28 mm showed only an insignificant decrease with treatment but there was striking clinical improvement enabling the patient to close the eyes the conjunctival injection disappeared and the patient was able to read again all this presumably on the basis of reduced intraorbital pressure This improvement has since been maintained following X irradiation of the orbits and male and female hormone therapy

The use of ACTH in both these patients had led to adrenal cortical stimulation as shown by a rise in 17 ketosteroid excretion to at least twice the control levels and a fall in eosinophils toward zero While the clinical effect on the exophthalmos and in one instance on the size of thyroid residue were marked and indisputable the measurable re duction in exophthalmos was negligible to absent

A simple theory must fit 3 main findings presented in this paper, viz Initial stimulation of I 131 uptake by the thyroid with adrenal steroids and suppression of this uptake in most instances upon pro longed adrenal cortical stimulation minimal effects in panhypopitui tarism a slight improvement in malignant exophthalmos with ACTH Stimulation of TSH secretion by small amounts of adrenal steroid or its decreased destruction following lympholysis and in contrast in hibition of TSH secretion by excess of cortical steroids would explain the effects observed The inability to show thyroid depression in every case of hyperthyroidism treated with ACTH clearly indicates the presence of other unknown factors in the adrenal steroid relationship

SUMMARY

In hypothyroidism the rate of adrenal cortical activation in re sponse to ACTH appears impaired

Compound E acetate Lipoadrenal Cortex at first increase and after 2 or 3 days decrease the rate of iodine uptake by the thyroid gland of patients with Addison s disease ACTH in a normal subject suppresses the rate of iodine uptake by the thyroid after 48 hours

Three of 4 cases of hyperthyroidism showed improvement in their disease under ACTH therapy (10 to 20 mg q 6 h i m) The failure was correlated with the longest duration of disease and the poorest 17 ketosteroid response The return to normal of the protein bound iodine and accumulation gradient of I 131 were the most remarkable findings in the successfully treated cases The size of the thyroid was markedly decreased and there was a fall in BMR ACTH was used as the sole preparation for thyroidectomy in one of the cases

Exophthalmos after thyroidectomy was markedly improved by

ACTH therapy in 2 cases although the measurable degree of proptosis was little altered

The inconstancy in the response of hyperthyroidism to adrenal cortical stimulation suggests the presence of unknown factors in the phenomena described The adrenal cortical effects on the thyroid function do not appear to present a reliable or practical form of therapy for hyperthyroidism

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	ACTH	
Name	*Pre*	*Post*
Myerson	4 8%	5 4%
Erickson	6 9	6 8
McShane	15 6	9 7
Fohroy	11 2	18 2
		12 5

Fig 4 ACTH

DISCUSSION

DR SIDNEY WERNER We heard about this work in Boston and having a deep investment in radioactive iodine in the therapy of hyperthyroidism we persuaded Dr Mote to let us have some ACTH to try

Unfortunately we struck 2 patients who did not respond to the hormone

From our experience I wish to emphasize 3 points First the lack of response to ACTH second, the fact that the accumulation gradient and the ultimate uptake of I at 24 hours do not necessarily mean the same thing, third a need for caution which so far I have not heard mentioned about toxic effects from ACTH side actions which are not minimal

In Fig 4 one can see pre and post values for serum precipitable

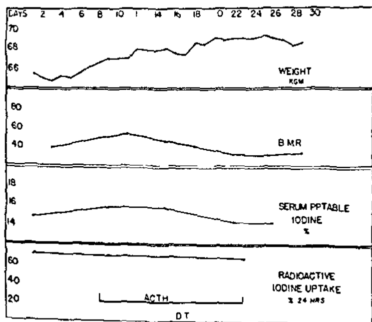


Fig 5

iodine at the end of 1 week of ACTH treatment for rheumatoid arthritis There also were unlisted values at the end of 28 days of treatment The serum precipitable iodine was done by the method of Barker, and of course the table should read micrograms % instead of per cent

There is no significant change in serum iodine level with ACTH therapy except in the case of McShane who turned out to have had lipiodol just before this treatment Radioiodine tracer uptakes were equally unaffected by ACTH

Fig 5 shows a patient with hyperthyroidism If you will look at the second column you will see that with treatment with 100 mg daily there was a steady rise in basal metabolism from about 45% to prac

tically 75% then a fall back to the original level During this treatment the patient developed an episode of hysteria The serum precipitable iodine fell somewhat, although I am not persuaded to a clinically significant extent The radioactive iodine uptake measured both at 2 hours and at 24 was more or less unchanged

Fig 6 shows another hyperthyroid patient in whom again there was the same early rise in basal metabolic rate following ACTH, with perhaps a slight rise in serum iodine level Absolutely no change in

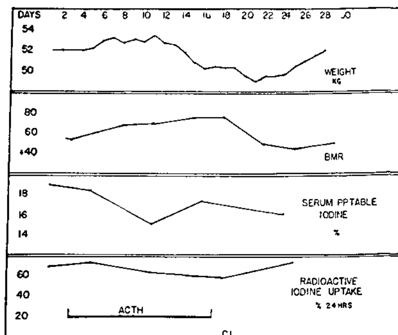


Fig 6

radioactive iodine uptake was noted at 2 and at 24 hours after I 131 administration

In Fig 7 we have tried to show a little about toxicity The blood pressure did rise in this patient The diastolic pressure reached 100 although the systolic pressure did not go much above 150 By the end of the experiment this patient had not yet shown any great effect on blood sugar level

In Fig 8 the next patient however not only showed a rise in blood pressure but developed a very severe hyperglycemia with a loss of over 100 grams in the sugar in the urine per day which at the present time is still present although the blood sugar has come back to normal 12 days after cessation of treatment There was a polyuria of 7,000 cc in 24 hours in the middle of this experiment

It should be mentioned as stated by Dr Forsham that the thyroid gland became impalpable in both our patients Despite this no clinical improvement was noted and as stated above laboratory evidence of any reduction of toxicity also was not achieved The temporary suppression of accumulation gradient noted by Dr Forsham is not reflected in the 2 and 24 hour uptakes of I 131 by the thyroid gland

DR F I ENGEL We can report on 1 case of hyperthyroidism treated with ACTH who got a good response with respect to improvement in

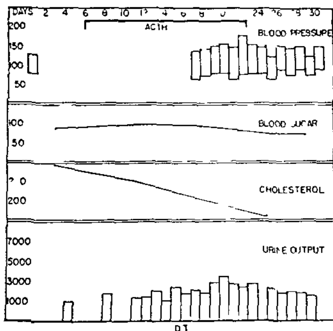


Fig 7

general condition with a fall in B M R from plus 44% to plus 4% in 10 days Incidentally this patient had auricular fibrillation and mild congestive failure when treatment was begun and it is of interest that his edema disappeared while he was getting ACTH He certainly did not get worse The patient lost weight steadily during 3 weeks of treatment and had glycosuria during the entire time

On the other hand this patient had very severe exophthalmos with exophthalmometric readings of 24 millimeters on one side and 23 millimeters on the other and there was absolutely no change in his eyes in the course of 2 weeks although the edema of his lids did improve

Three weeks after discontinuing the hormone, the patient had gained 28 pounds representing a net gain of 5 pounds over his admission weight when he had edema The B M R was +15% and the patient had no evidence of hyperthyroidism The exophthalmos was as marked as before and some edema of lids had recurred Fibrillation persisted but there was no evidence of congestive failure

DR GEORGE W THORN What was the dose of ACTH Dr Werner?

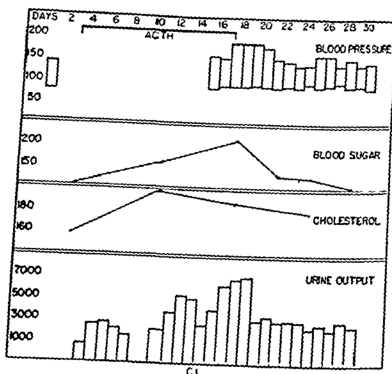


Fig 8

DR SIDNEY WERNER 100 mgs a day I should mention that the gland did practically disappear

DR JEROME W CONN Inasmuch as we have found and have reported a very profound fall in serum cholesterol of normal people under the influence of ACTH I wonder whether Dr Forsham has found any change in the serum cholesterol as the b m r was coming down in the hyperthyroid patients?

DR PETER H FORSHAM I would like to take this opportunity to express my gratitude to you Dr Conn for that particular point for a personal

reason For when it was decided what to do with these patients the number of determinations people wanted done was rather considerable and when it came to doing cholesterol and cholesterol esters I pointed to your paper and said that any fall or rise in cholesterol would not mean anything because of the fall you observed following ACTH Thus, one could not relate any of the changes in serum cholesterol directly to the control of hyperthyroidism Consequently we did not do cholesterols on those patients

DR R W RAWSON Dr Thorn I am intrigued by your statement that the adrenal in Graves disease is so overworked I would have thought that the adrenal was incapable of responding in these patients Indeed, in my own mind I have thought of Graves disease as a syndrome which has developed in part as a result of adrenocortical insufficiency

The anatomical evidence observed in patients who have died of Graves' disease which suggests an adrenal insufficiency is enlargement of the lymph nodes and thymus and adrenal cortices which are smaller than normal These small adrenals are to be contrasted to the enlarged adrenals which occur in rats treated with large doses of thyroid and which we should find if the adrenals of patients with this disease were being stimulated by the hyperthyroidism of this disease

Experiments that Dr Nathanson and Dr Brues and I did about 10 years ago would indicate that the thyroid is more sensitive in the absence of the adrenal Immature female rats treated once with 5 mgm of testosterone showed a significant hyperplasia of the thyroid about 96 hours following the injection If the adrenal was absent the hyperplasia was much more intensive

Dr Soffer has reported that the same thing occurs with adrenalin stimulated animals We have observed almost identical results with those reported by Dr Soffer in similar experiments

I cannot get excited by the theory that adrenal hormones act to release bound TSH from the lymph nodes Indeed the evidence does not suggest that the hormone is bound by the lymph nodes only that it is inactivated by lymph nodes

Finally no matter what apparently new theories we advance I think it desirable to point out that Marine first suggested that Graves disease is a syndrome of adrenal insufficiency about 25 years ago The studies reported this afternoon by Dr Thorn and his associates again indicate that Dr Marine was consistently a quarter of a century ahead of his time

DR ABBIE KNOWLTON (College of Physicians and Surgeons Columbia University New York) We have observed as has Dr Forsham that patients with hypothyroidism exhibit a diminished response to a single

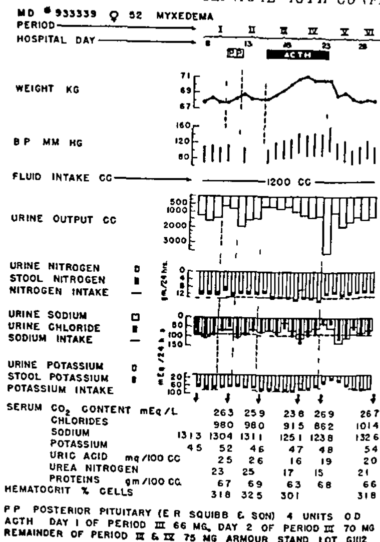


Fig 9

injection of adrenocorticotrophic hormone as measured by the percentage decrease in circulating eosinophils

This raises the question as to whether in myxedema there exists a state of decreased adrenal activity Margitay Becht s report of routinely low serum sodium values in hypothyroidism and more recent studies which indicate that corticoid excretion in the urine is diminished in myxedema both tend to support this hypothesis

We were interested to determine the effect of continued ACTH (Armour) administration on such a hypothyroid individual and have given ACTH to 1 patient with myxedema on two occasions for 7 and 8

D #(3333) A 5 YEAR OLD FEMALE MYXEDEMA [illegible]

Period	Day	Wt (kg.)	Fluid Balance: Intake	Fluid Balance: Urine	Fluid Balance: Av. Daily Balance per Period	Sodium Balance mEq: Intake	Sodium Balance mEq: Urine	Sodium Balance mEq: Stool (Aver.)	Sodium Balance mEq: Av. Daily Balance per Period	Chloride mEq: Intake	Chloride mEq: Urine
I P	9 1 13	67 5 68 25 67 75	1200	1250 154 1610 650	12	92 8	85 7 105 2 89 6 67	5 6	+6 6	100 0	89 110 9 97 2 69
II	12 13 14 5	6 26 68 68	1 00	800 80 1560 1460	-250	91 6	65 104 4 66 6	2 8	+9 5	1 1 3	59.4 108 2 96 8 8 9
III CTH	6 18 19	68 13 68 5 9 34 70 14	1200	700 33 800 700	468	93 93 6 94 94	75 5 30 0	2 2	29 0	98 1	82 8 71 6 91 55 5
IV CTH	20 21 3	70 59 06 70 60 70 5	1200	040 1260 1370 2300	3	94 3 85 3* 93 3	6 5 5 7 63 0		1 6	98 89.6* 98 4	132 2 119 8 1 1 4 87 1
	24 5 26 27	0 66 68 66 9 68 43	1200	1440 080 1340 1680	835	86 6	36 5 5 77 9	4 3	-0.4	95 1	29 8 39 5 115 0 96 9
VI	28 29 30	68 11 68 5 68 13	1200	345 5 1435	-232	88 6 95 9	51 80 72 9	8	2.6	95 1 101 0	63.4 92 6 93

Period	Potassium Balance mEq: Intake	Potassium Balance mEq: Urine	Potassium Balance mEq: Stool (Aver.)	Potassium Balance mEq: Av. Daily Balance per Period	Nitrogen Balance gm.: Intake	Nitrogen Balance gm.: Urine	Nitrogen Balance gm.: Stool (av.)	Nitrogen Balance gm.: Av. Daily Balance per Period	17 Ket. mg	Urine Creatinine gm.	17-Ketosteroids Daily Average mg	*Corticoids Daily Average mg
I P	80 1	57 1 66.4 69.4 6	12 4	+7 1	13 90	10 40 10.65 10 68 .21	1 40	+2 32	526 55 39 4	1 23 1 3 1 8 93	2.4 3 1	0 7 0 3
II	8 7	59 6 95 4 63 6 3 1	4 2	22 2	13.47	11 30 1 93 10 53 10 62	1 16	1 65	642 545 79 576	1 21 1 18 1 5 1.20	3 9	0 5
III CTH	82 8	71 7 71 6 2 76.4	8 4	+0 9	13 85	10 01 12 56 12 76 12 74	0 87	+0 91	790 812 731 695	1.20 1 20 1 22 1 17	5 1 5	0 6 ?
IV CTH	87 6 9* 75 3	76 6 72.4 87 5 59 3	6.4 6 3	3 7	13 85 8 71 13 57	14 27 3 20 13 92 14 65	0 87 0 58	-2 13	724 667 641 702	1 18 1 6 1 20 1 21	11 9	3 3 3
	70	37 5 5 1 27 9 53 8	7.4	29 9	13 60	1 92 1 75 11 77 10 58	0 92	18.8	431 3 3 692 454	1 01 1.06 1 10 1 12	7 6 7 1	1.4 1 2
VI	70.2 8 7	71 3 4 72 6	4 0	+0 9	11.60 13 0	10 16 92 10 15	0 45	+2 67	659 635 637	1 20 1 13 1 15	7 3	0 6
									Ten day late		5 5	1 1

Fig 10 Explanations

1 P P = Posterior pituitary (E R Squibb & Son) 4 units daily

2 ACTH = Day 1 of period 3—66 mg day 2 70 mg day 18–23, 75 mg Armour Standard—Lot H 2303

* Patient refused supper Rejected food analyzed and subtracted from daily intake

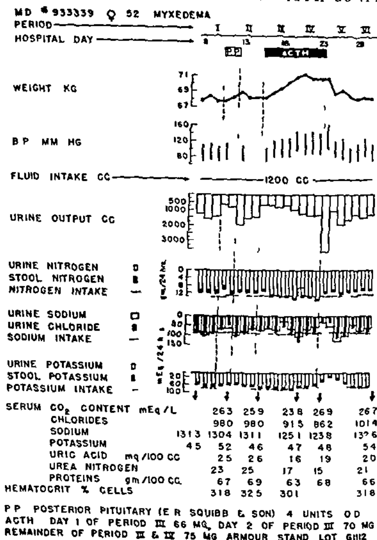


FIG 9

injection of adrenocorticotrophic hormone as measured by the per centage decrease in circulating eosinophils

This raises the question as to whether, in myxedema, there exists a state of decreased adrenal activity Margitay Becht s report of routinely low serum sodium values in hypothyroidism and more recent studies which indicate that corticoid excretion in the urine is diminished in myxedema both tend to support this hypothesis

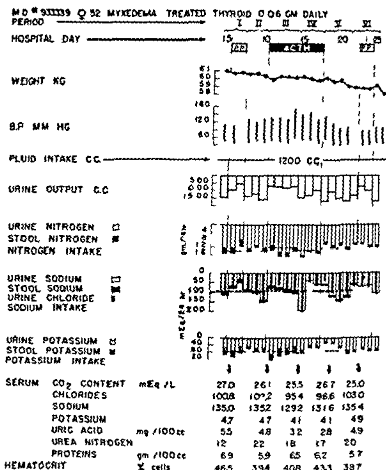
We were interested to determine the effect of continued ACTH (Armour) administration on such a hypothyroid individual and have given ACTH to 1 patient with myxedema on two occasions for 7 and 8

D #933339 A 5 YEAR OLD FEMALE [illegible]

Period	Hours [illegible]	[illegible]	Fluid Balance In	Fluid Balance Dr	Av Daily Balance per period	Sodium Balance mEq Intake	Urine	Stool	Daily Balance per period	Chloride mEq Intake	Urine	Potassium Balance mEq Intake	Urine	Stool	Av Daily Balance per period	Nitrogen Balance gm Intake	Urine	Stool	Av Daily Balance per period	[illegible] mg	[illegible] gm	17-ketosteroids mg	Corticoids average mg
I PP[1] PP	5 6	61 60 60 87	1 70	1460 34 5	22	94 9	97 8 66 3 28 2	1 7	13 0	96 3	97 3 0 3 8	9	6 64 8 5 2	28 9	14 9	13 5	12 00 1 1 1	2 99	-0 21	424 2	80 90 52		1 2
II	8 9	60 62 60 9 60 44	1 00	1360 122 600	89	94 9	81 6 1 8 139 5	5 2	14 6	96 3	80 6 104 133	0	6.4 5 56 3		1	13 5	12 6 1 90 1 20	1 3	+0 84	86 581 9	87 2 89	4	1 5
III ACTH[2]	1 2** 3** 16	9 3 60 35 60 31 60	1	0 30 60	44	95	65 1 68 82 8 86 8	14 3	5 2	97 5	69 60 48 98	69 0	85 6 60 55 0 44 7	32 0	-26.8	11	1 5 14 14 40 11 65	05	3 3	793 6.9 [illegible] 64	46 8 1	4 3 / 6	1 4 / 2
ACTH[3]	5 6 17	60 35 60 3 5 80	200	1477 3 960	-6	97 / 98	3 5 8		44 5	1 3	104 7 5 8	7 8	46 2 42 5	5 5	1	13.4	16 3 14 20	1 3	63	900 84 3	2 82 82	1 5	3 8
	8 9 1	60 09 5 62 5 84 5	1200	00 130 1 20 680	100	94	09 3 6		12	99 0	33 2 96 4 24 5 1	67 5	17 7 21.4 3 76	8 4	1 0	11 8	9 20 11 30 90 00	9	-0 39	962 62 627 86	46 7[illegible]	2 3 / 6	1 8 / 1 6
VI R***	3 24 5	58 90 5 92 58 84 34	600	300 10 000 1680	33		5 64 60 8 97	1			66 70 9 137		68 1 5 8 64 3 62	8 2			80 9 60 1 30 1 10			676 69 568	89 3 86 89	5	9
	6	8 00																					

Fig 12 Explanations

1 P P = Posterior pituitary (E R Squibb) 4 units daily
2 ACTH = 72 mg daily Armour Standard Lot H 2303 for first 5 days
3 ACTH = 75 mg daily Armour Standard Lot G 1112 for last 2 days
* = ? Amount of urine included in loose stool *Two loose stools this day*
** = Seven stool specimens, loose in these two days
*** = R thyroid 60 mg daily



SERUM CO_2 CONTENT	mEq /L	27.0	26 1	25.5	26 7	25.0
CHLORIDES		100.8	10?.2	95 4	96.6	103 0
SODIUM		135.0	135 2	129 2	131 6	135 4
POTASSIUM		4.7	4 7	4 1	4 1	4 9
URIC ACID	mg /100 cc	5.5	4.8	3 2	2.8	4.9
UREA NITROGEN		12	22	18	17	20
PROTEINS	gm /100 cc	6 9	5.9	6.5	6.2	5 7
HEMATOCRIT	% cells	46.5	39.4	40.8	43.3	38 7

P P = posterior pituitary (E R Squibb & Son) 4 units Q.D.
ACTH 72 mg Armour Standard Lot H2303 daily for 5 days
75 mg Arm Standard Lot G1112 daily to 6th and 7th day

Fig 11

days respectively in the dosage of 66–75 mg a day The initial balance study was undertaken prior to giving any thyroid medication (Figs 9 and 10) and the second study was made 3 months later (Figs 11 and 12) when evidences of myxedema had cleared as a result of thyroid therapy

A similar increase in nitrogen excretion occurred in both periods of ACTH administration, while changes in carbohydrate tolerance were equivocal In both instances the withdrawal of ACTH was followed by a period of potassium retention In both studies a similar increase in uric acid excretion ensued and similar increases in 17 ketosteroid excretion were observed When myxedematous the ex

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Results of ACTH in One Patient with Thyrotoxicosis and Thyrotoxic Heart Disease with Mild Congestive Heart Failure

Arthur J Moseley and Arthur J Merrill

GRADY MEMORIAL HOSPITAL AND EMORY UNIVERSITY SCHOOL OF MEDICINE ATLANTA

The patient was a 32 year old colored female with a history of thyrotoxicosis of 3 years duration She had previously been controlled with propylthiouracil but had discontinued medication 1 year prior to the present study and for 6 months preceding the study the symptoms of thyrotoxicosis had reappeared and were progressive Associated with these symptoms were pedal edema orthopnea and exertional dyspnea X ray of the chest revealed cardiac enlargement and pulmonary congestion

The patient was placed on a standard 400 mg sodium diet containing approximately 3000 calories and 110 Gm protein plus 6 0 Gm added sodium chloride daily After a 4 day control period 25 mg ACTH (Armour) was given every 6 hours for 5 days except for the unintentional omission of the 2 00 P M dose on the fifth day This treatment period was followed by a final 5 day control period Calculation of the urinary excretion products on the third treatment day were estimated since some urine was spilled

No definite change in clinical status of the patient could be detected However 4 days after ACTH was discontinued the BMR was +38 as compared with a control level of +59, but rose to +61 8 days later The blood cholesterol which had risen from 128 mg % to 149 mg % during the initial control period continued to rise on ACTH to 169 mg % on the last day of administration Then during the final control period cholesterol level receded to 153 mg %

The fall in blood eosinophile count while on ACTH was only about 50% until the last day of administration when the count dropped to 5% of control level Following the discontinuation of ACTH the eosinophiles promptly returned to control values The blood sugar levels were only slightly affected

cretion of corticoids during control periods was less than it was when the patient was euthyroid but the percentage increase during ACTH administration was comparable on both occasions

No significant change in basal metabolic rate or in serum cholesterol levels was observed in either period of ACTH administration (Fig 13)

M D — Myxedema					*D D — Myxedema Treated*			
Days	*ACTH mg per Day*	*BMR %*	*Serum Cholesterol mg %*	*% I_2 Uptake*	*Days*	*ACTH mg per Day*	*BMR %*	*Serum Cholesterol mg %*
4	0	−22	338	2	3	0	−1	257
4	0	−21	348	–	3	0	−13	220
4	66–75	−17	300	–	4	72	−8	220
4	75	−20	325	0	3	72–75	−9	—
4	0	—	304	–	4	0	—	215
3	0	−23	—	–	4	0	−17	210

Fig 13

The 2 studies on this one patient indicate that with the continued administration of ACTH evidences of increased adrenal activity may be observed in the presence of hypothyroidism and these changes are quantitatively comparable to those seen in the euthyroid state

DR LAURANCE W KINSELL I would like to make just one comment in regard to Dr Knowlton s comments It would seem probable to me that the responsiveness of the adrenal cortex in the patient with myxedema would probably be delayed but still would be perfectly within the normal range and that perhaps the difference in her observations related to the greater prolongation of the period of study

18

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4	0	—	304	–	4	0	—	215
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second day of ACTH the excretion values were 23 mg per 24 hours and 28 mg per 24 hours respectively, thereafter the excretion remained between 10 and 15 mg per 24 hours

During the initial control period the renal plasma flow was 812 cc per minute On the fourth day of ACTH the value was 641 cc per minute a fall of 21% which is probably a significant drop The day after ACTH was discontinued the renal plasma flow was found to be 908 cc per minute Simultaneous determination of the glomerular filtration rate was attempted but the results could not be interpreted because of technical difficulty

Sweat sodium concentration, supposed to indicate DOCA like activity level, which was initially at the lower limit of normal 22 mEq per liter was found to be definitely low at 14 mEq per liter on the second day of ACTH Seven days after treatment was discontinued sweat sodium value was 29 mEq per liter

There were no significant changes in blood urea, serum uric acid, serum sodium, chloride or phosphorus values

Fig 1 depicts the changes in water balance weight, and certain urinary excretion products In the construction of the water balance graph, intake is plotted downward from the zero line and output plotted upward from the intake level Thus positive balance is repre

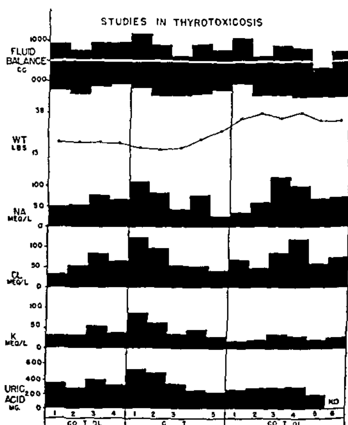


Fig 1 Studies in thyrotoxicosis

sented below the zero line and negative above The urinary sodium excretion rose during the first day of ACTH (Armour), but fell progressively during the remainder of the period of ACTH administration with a sharp rebound when ACTH was discontinued Urine chloride changes were similar to those of sodium Urine potassium and uric acid excretion were increased only during the first 2 days of ACTH Although not shown on the figure 17 ketosteroid excretion behaved similarly to that of potassium and uric acid The control 17 ketosteroid excretion was 14 6 mg per 24 hours On the first and

steroids attained a value which is roughly that found in a normal woman (7 7 and 8 0 mg/24 hrs), while the 11 oxysteroids † attained a value about 7 times the normal

In the patient with ovarian agenesis (Fig 2), the 17 ketosteroids attained a value roughly 3 times that found in a normal woman

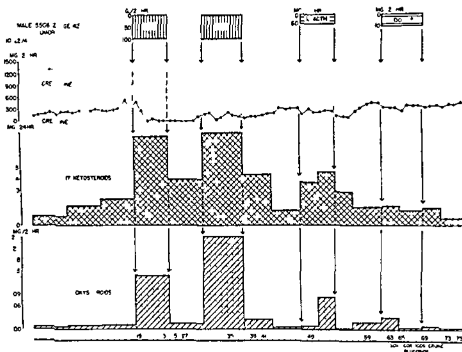


Fig 1 Patient H J M G H #550872 male 42 with panhypopituitarism Plan of study and urinary creatinine creatine 17 ketosteroids and 11 oxysteroids during treatment with ACTH Armour ACTH Li and desoxy corticosterone glucoside

(27 mg/24 hrs) while the 11 oxysteroids † again attained a value about 7 times the normal

In the patient with acromegaly (Fig 3) the 17 ketosteroids attained a value roughly 11 times that found in a normal woman (115 mg/24 hrs) while the reducing steroids‡ again attained a value about 7 times the normal In this last experiment a lower dosage of ACTH (72 mg) was given for the first 6 days than that (100 mg) given in the last 6 and in the other 2 experiments

† Determined by Dr Nathan Talbot Normal value about 0 3 mg/24 hr
‡ Determined by Dr Lewis Engle Normal values—Aqueous (A Fig 3) about 1 5 mg/24 hrs Crude (C Fig 3) about 3 mg/24 hrs

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A Comparison of the Effects of ACTH in Panhypopituitarism, Ovarian Agenesis, and Acromegaly

Frederic C Bartter,[1] Anne P Forbes and Fuller Albright

MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

In panhypopituitarism in which the adrenals are atrophic and the excretion of 17 ketosteroids is very low one would expect a markedly subnormal response to ACTH In ovarian agenesis, in which the adrenals have been reported to be smaller than normal and the excretion of 17 ketosteroids is below normal one would expect a slightly subnormal response to ACTH In acromegaly, in which the adrenals are large and the excretion of 17 ketosteroids of adrenal origin is in the upper normal range one would expect a greater than normal response to ACTH

This is a comparison of the effects of ACTH in one patient with each of these syndromes * given comparable amounts of ACTH for comparable periods of time

A Steroid Excretion

Figs 1, 2 and 3 show the results of urinary steroid determinations and the design of each experiment (In the first experiment [panhypopituitarism see Fig 1] we are here concerned with the two courses of ACTH Armour and will not discuss the effect of ACTH Li or of DOCG in the second experiment [ovarian agenesis see Fig 2] we will not discuss the effect of APL in the third experiment [acromegaly see Fig 3] we will not discuss the effect of estradiol dipropionate)

The order of magnitude of the rises in steroid excretion in these 3 patients was as follows

In the patient with panhypopituitarism (Fig 1) the 17 keto

[1] Surgeon U S P H S National Heart Institute on detail at Massachusetts General Hospital

* Patient M K with ovarian agenesis received 1 mg a day of stilbestrol throughout the study In a later study on this patient (not here reported) the same amount of ACTH was given without stilbestrol The results for the metabolites reported in this study were not significantly different in the absence of stilbestrol

scales for K and N are in the same proportion as the K and N contents of protoplasm (muscle), thus it may be seen visually that these changes in K are very much larger than any comparable changes of protoplasm as estimated from the N data

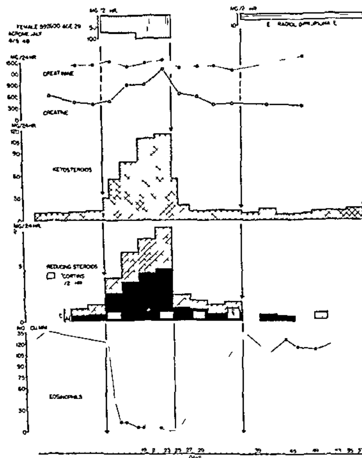


FIG 3 Patient E B M G H #592600 female 29 with acromegaly Plan of study urinary creatinine creatine 17 ketosteroids reducing steroids (A = Aqueous fraction C = Crude fraction) biological cortin (M U = mouse units) and circulating eosinophils during treatment with ACTH Armour and estradiol dipropionate

C Effect on Nitrogen (N) Balance

In Figs 7 8 and 9 (top panel) are shown the alterations in N balance in these experiments In the patient with panhypopituitarism negative N balance developed relatively slowly and the overall loss

B Effects on Sodium (Na), Chloride (Cl), and Potassium (K)

Figs 4, 5, and 6 show the alterations in Na and Cl metabolism in these experiments ACTH produced, in the patients with panhypopituitarism (Fig 4) and ovarian agenesis (Fig 5), marked retention

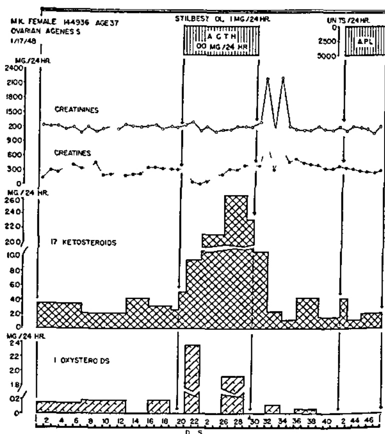


Fig 2

of Na and Cl in the patient with acromegaly only moderate retention of these ions Since the basic diets were of different compositions *a quantitative comparison of these effects is not possible* In all cases there was a marked rebound loss of Na and Cl when ACTH was stopped

In Figs 7 8 and 9 (bottom panels) are shown the alterations in K balance in these experiments There is a striking similarity in all of them In each instance a marked transitory loss of K occurs on the first day of ACTH administration and a marked transitory retention of K occurs within the first 2 days after it is stopped The relative

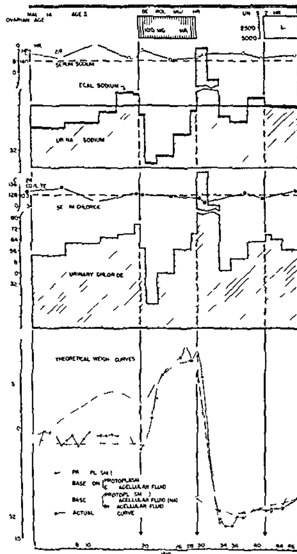


Fig 5 Ovarian agenesis (see Fig 2) Serum sodium and chloride sodium balance urinary chloride and theoretical weight curves

during 6 days was 16 and 12 grams during the two courses of ACTH In the patient with ovarian agenesis the negative N balance developed more rapidly and the overall loss during 6 days was 18 4 grams In the patient with acromegaly negative N balance developed

final level will be below the base line Thus a negative balance is indicated by a shaded area above the base line and a positive balance by a clear area below the base line

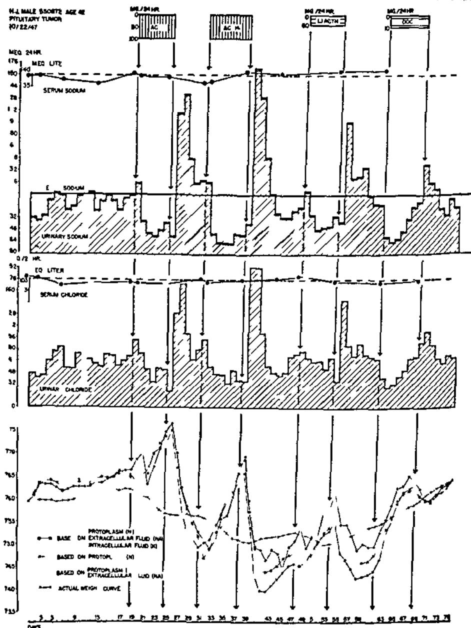


FIG 4 Panhypopituitarism (see legend to Fig 1) Serum sodium and chloride sodium balance urinary chloride and theoretical weight curves

The sodium balance (and other balance data given in this study) are charted as follows

There is a horizontal base line intake is charted downward from this base line the urinary and fecal excretions are then measured upward from the intake line towards the base line If the output (fecal and urinary) exceeds the intake the final level will be above the base line if it does not the

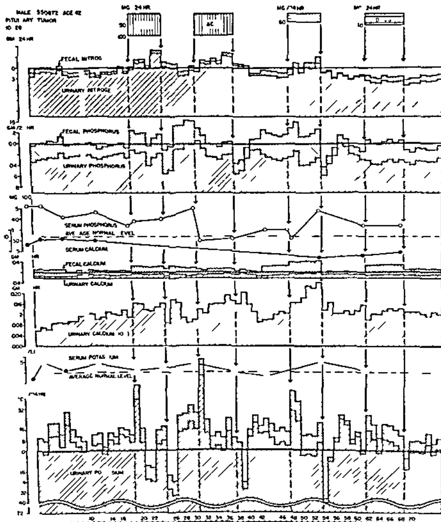


FIG 7 Panhypopituitarism (see legend to Fig 1) Nitrogen phosphorus calcium and potassium balances and serum P Ca and K The data for Ca and P are not discussed

In Figs 7 8 and 9 the scales for N P Ca and K metabolism are chosen that (for changes in protoplasm and bone) the area representing P balance should equal the sum of the corresponding areas for N and Ca and that representing K balance should equal that for N

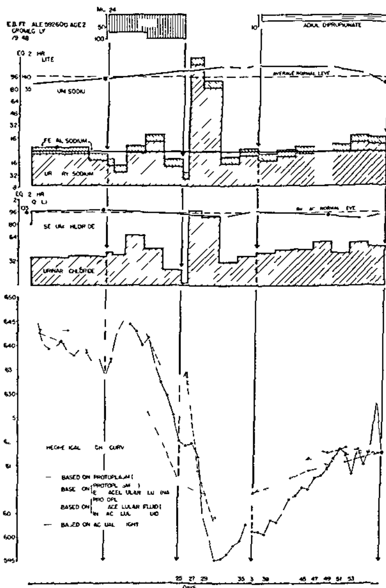


FIG 6 Acromegaly (see legend to Fig 3) Serum sodium and chloride so dium balance urinary chloride and theoretical weight curves

very rapidly and the overall loss during 6 days was 29 7 grams (it will be remembered that this patient received a lower dosage during these 6 days) In no experiment however did significant negative N bal ance occur on the first day, the day of the marked K diuresis

In conclusion then in these 3 patients the rises in reducing steroids produced by comparable amounts of ACTH were of the same

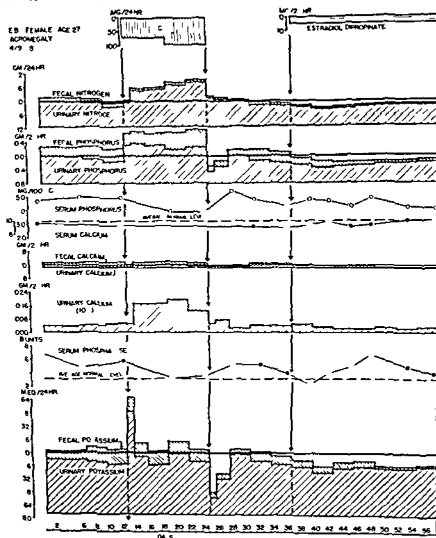


Fig 9 Acromegaly (see legend to Fig 3) Nitrogen phosphorus calcium and potassium balances and serum P Ca and alkaline phosphatase

DISCUSSION

DR NATHAN B TALBOT May I ask what this correlation was? Was it a positive or a negative correlation?

DR FREDERIC C BARTTER Positive The higher the ketosteroids the greater the nitrogen loss

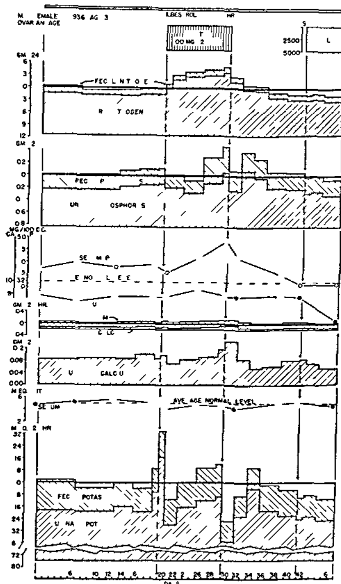


FIG 8 Ovarian agenesis (see legend to Fig 2) Nitrogen phosphorus calcium and potassium balances and serum P Ca and K

order of magnitude The rises in 17 ketosteroids on the other hand did increase in the order in which we had expected from what we know of the 3 disease syndromes

The metabolic effects on sodium chloride and potassium were quite similar in all 3 patients but the extent of the negative nitrogen balance was quite well correlated with the 17 ketosteroid excretion

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The Metabolic and Clinical Effects of Pituitary Adrenocorticotrophic Hormone in Spontaneous Hypoglycemosis

Irvine McQuarrie E G Bauer M R Ziegler, and W S Wright

UNIVERSITY OF MINNESOTA HOSPITAL AND UNIVERSITY OF MINNESOTA MEDICAL SCHOOL MINNEAPOLIS

Spontaneously occurring persistent hypoglycemia of severe grade with such manifestations as repeated convulsions or attacks of coma and irreversible damage to the central nervous system is fortunately not a very common disorder On the other hand milder forms of the condition characterized by such symptoms as a vague sensation of hunger or gauntness a feeling of faintness or weakness limpness cold sweats pallor and other vasomotor reactions tremulousness dizziness mental confusion drowsiness and occasional convulsions occur with far greater frequency than is generally appreciated It has been estimated by several authorities[1] on the subject that the total number of persons who are afflicted with the syndrome of spontaneous hypoglycemosis (hypoglycemic state) is almost as great as the number known to suffer from diabetes mellitus

Because of the mildness or vagueness of the symptoms and their irregular occurrence as well as the prompt relief obtained from ingestion of even small amounts of carbohydrate many individuals afflicted with the milder form may never seek medical assistance unless the symptoms become progressively worse or they may do so only after suffering from the disability over long periods of time When consulted concerning such a patient the average physician finding no signs of physical disease is inclined to interpret the symptoms as manifestations of a psychoneurotic state unless the possibility of hypoglycemosis perchance occurs to him and is confirmed by fasting blood sugar determinations glucose and insulin tolerance tests and other diagnostic studies

While the primary disease responsible for spontaneous hypoglycemia can often be diagnosed from the clinical history the physical

DR ROGER A LEWIS I would like to give Dr Bartter permission to hypothecate on the loss of potassium in this particular instance You can see the nitrogen loss was greater than the sodium retention Why did you have such a large loss of potassium on the first day?

DR FREDERIC C BARTTER I wish we could answer that Dr Lewis Maybe someone else will? I don t know

DR ROY HERTZ I think it is ill advised to generalize regarding char acteristics of metabolic disturbances on the basis of one case At the present time we have on hand a case of ovarian agenesis proven by biopsy of the ovarian anlagen in which the ketosteroid secretion is normal and the gonadotrophic hormone complex in the urine is within normal range *

VOICE Did the patient with acromegaly have diabetes?

DR FREDERIC C BARTTER No During treatment she excreted up to 21 grams a day of urinary sugar

* The authors wish to point out that decreased urinary 17 ketosteroid excretion (and elevated follicle stimulating hormone excretion) were present in all of the eleven cases reported from their clinic

several such benign tumors total excision of the neoplasms may result in complete cure Carcinoma arising from the beta cells naturally presents a much more serious surgical problem The prognosis is hopeless if widespread metastases are present Subtotal resection of the pancreas may at times give satisfactory results in patients with relative hyperinsulinism of the idiopathic type and even in those with benign hyperplasia of the islet tissue Alloxan used as a last resort by Talbot and co workers[3] in one severe case of hyperinsulinism to reduce the beta cell activity, appeared to give satisfactory results Because of its marked hepatotoxic and nephrotoxic action however this agent if used at all should obviously be used with extreme care

For those patients who suffer from adrenocortical insufficiency or pituitary insufficiency specific replacement therapy (adrenocortical and adrenocorticotrophic hormones respectively) and avoidance of fasting are indicated The most important feature of the therapy for hypoglycemosis due to the various forms of liver disease is that which is directed to the primary disease itself In the milder intermittent forms of so-called functional hypoglycemia the etiology of which may be entirely obscure use of the high protein comparatively low carbohydrate diet recommended by Conn[4] may suffice to control the blood sugar level

The hypoglycemic patients presenting the most bewildering therapeutic problem however are those who suffer from severe and persistent hypoglycemia of undetermined cause despite the use of a high protein low carbohydrate or a high fat low carbohydrate dietary regimen and other conservative forms of treatment Even removal of large fractions (80 to 85%) of the normal pancreatic tissue may give only temporary relief which was the result in 3 cases (1 adult 2 young children) studied and treated at our institution

Several years after it was announced by Corey and Britton and by Long[6] that adrenal cortical extract in excessive dosage exerts a diabetogenic effect in normal animals we attempted to apply this new information by administering comparatively large doses of commercially available adrenal cortical extracts to young children suffering from spontaneous hypoglycemia of non Addisonian type While the results in a few instances were mildly encouraging they were not sufficiently definitive to justify the expense entailed in extensive use of the extract At the present time however we are engaged in a re investigation of the effects of whole cortical extract on severe hypoglycemia using a highly concentrated product (Lipo Adrenal Extract—Upjohn)

On the basis of the well known observations by Houssay Evans[8] Marine[9] Young[10] and their co workers that continued administration of crude extracts of the anterior lobe of the pituitary gland produces

examination and fasting blood sugar studies alone, it may be necessary to conduct more elaborate laboratory tests to ascertain what organ functions are involved In many instances, however the primary etiology or pathogenesis remains obscure even after all available diagnostic procedures including exploratory laparotomy, have been exploited

The expression absolute (or true) hyperinsulinism ' obviously implies overproduction of insulin by the beta cells of the pancreas or therapeutic overdosage While it is conceivable that normally appearing insular beta cells might produce excessive amounts of insulin at times in response to extra pancreatic stimuli the evidence that this is an important cause of spontaneous hypoglycemia in any but the mildest cases is not convincing Tumors (adenoma and carcinoma) and hyperplasia involving the beta cells of the pancreatic islands constitute the only satisfactorily demonstrated pathological lesions associated with absolute hyperinsulinism Tumors are extremely rare in children They occur with greater frequency in adults Hyperplasia of the islet tissue occurs more frequently in young children than do discrete tumors but it is not the most common cause of spontaneous hypoglycemosis

The term relative hyperinsulinism refers to the state in which hypoglycemia results not from over production of insulin but from under activity of one or more of the organ systems which is antagonistic to insulin Hypocorticoadrenalism (Addison s disease) anterior pituitary deficiency (Simmond s disease and certain cases of pituitary dwarfism), extensive liver disease (necrosis atrophy acute hepatitis, cirrhosis and von Gierke s glycogen storage disease) are the most commonly recognized primary disease entities causing relative hyperinsulinism In these clinical conditions the hypoglycemia is characterized by its appearance almost exclusively at times most remote from meals indicating a deficiency in the glycogen stores of the liver or a deficiency in the mechanism for breakdown of glycogen to glucose (glycogenolysis) as in von Gierke s disease The net clinical significance of deficiencies in the cellular activity of the thyroid *posterior pituitary adrenal medulla and alpha cells in the islets of* Langerhans and of disturbances in the functions of the hypothalamus as regards the production of hypoglycemia cannot be accurately appraised at the present time Future investigations on these aspects of the problem will undoubtedly shed new light on the pathogenesis in patients with hypoglycemia of the so called ' idiopathic type, the most common form encountered in infancy and early childhood

Treatment of the different types of spontaneous hypoglycemosis naturally varies with the etiology In the comparatively rare cases which are due to a solitary beta cell adenoma of the pancreas or to

normally appearing pancreas removed at another hospital No hypo glycemic reactions for several months, following this procedure At 22 mon hs of age he had a recurrence of symptoms and a severe gen eralized convulsion after he had been eating poorly for several days Examination on admission to University of Minnesota Hospitals at that time (1945) was negative except for definite evidence of mental retardation Fasting blood sugar values were found to be 26 21 33 and 24 mgm % on successive days Attempts to elevate the fasting blood sugar and prevent convulsions by use of large doses of cortin and special dietary regimens were not successful In November 1946, a second partial pancreatectomy was done approximately 15% of the gland being retained Subsequent fasting blood sugar values ob tained elsewhere were reported to be 54 66 and 68 mgm % Learned to walk at age 4½ years but never talked Estimated mental age 1 year No recurrence of outspoken signs of hypoglycemia except for one convulsion When he was readmitted for present study the fasting blood sugar was found to vary between 30 and 54 mgm % from day to day

Case 2

B G sister of J G was seen first on November 8 1948 at the age of 7 months She had appeared to be entirely normal up to October 26 1948 On that day immediately preceding a meal she had a generalized convulsion similar to those experienced by her brother This lasted 15 minutes A second prolonged convulsion occurred on November 4 Between that time and November 8 she had 3 minor spells characterized by clouding of consciousness and inability to focus her eyes for a short time

Physical and neurological examinations were quite negative ex cept for a moderate degree of undernutrition, hypotonicity of the muscles and increased irritability Fasting blood sugar values were found to range between 15 and 40 mg % She was placed on a high protein low carbohydrate diet with frequent feedings but the hypo glycemic reactions were not affected by this regimen She was re admitted to the Hospital on several occasions because of frequent episodes of irritability staring loss of consciousness As a last resort an estimated 85% of her normal appearing pancreas was removed on February 15 1949 After 3 weeks of complete relief from symptoms she was discharged from the Hospital However the blood sugar level had already fallen to 47 mg % Less than 6 weeks after the operation severe hypoglycemic reactions had recurred despite trials on various types of diet Because the fasting blood sugar continued to range be tween 16 and 30 mg % she was readmitted to the metabolic ward for the present investigation The results of a preliminary histological study of the pancreas of this patient and that of her brother being

glycosuria and hyperglycemia (diabetogenic effect) in normal experimental animals we attempted in 1939 and 1940, to treat two young hypoglycemic patients with some of the then available commercial extracts of this gland One of these patients (age 13 years), a typical pituitary dwarf who had had generalized convulsions on several occasions when his fasting blood sugar was found to be in the neighborhood of 20 mg % appeared to show some improvement in the control of his blood sugar level while receiving large doses of growth gonadotrophic hormone preparations Morning convulsions ceased to occur and his fasting blood sugar was found to be only slightly below normal on two occasions when he returned to the Outpatient Department for rechecking The other patient a younger child suffering from what was diagnosed as idiopathic hypoglycemia in severe form, showed questionable improvement

When adrenocorticotrophic hormone was isolated in a comparatively purified form in 1943 from sheep pituitaries by Li, Evans and Simpson[11] and from hog pituitaries by Sayers White and Long[1] and was found shortly thereafter by Browne[13] to induce hyperglycemia and glycosuria in a normal man receiving a single large dose it became apparent to us that its effect on spontaneous hypoglycemosis should be studied as soon as adequate supplies of the purified hormone could be obtained The desirability of such a study became still more apparent when Conn Lewis and Wheeler[14] reported producing temporary diabetes mellitus in normal adult subjects by intensive intramuscular administration of the hormone over a period of several days

Early in the present year we were fortunate in obtaining a supply of the purified pituitary adrenocorticotrophic hormone at a time when we had at hand as promising experimental subjects 5 young children who were suffering from severe to moderately severe spontaneous hypoglycemosis A fairly comprehensive study of the clinical and metabolic effects of the ACTH was made in these cases Results of the investigation are reported below

CASE HISTORIES OF EXPERIMENTAL SUBJECTS

Case 1

J G, a 5½ year old white male At age 4½ months he developed wilting spells with a blank stare followed by rolling of eyes At 5½ months first generalized convulsion occurred Such attacks continued at about 6 week intervals in spite of phenobarbital and Dilantin therapy Regarded as normal infant otherwise At 16 months of age he was found to have fasting blood sugar of 27 mgm % Attacks relieved by glucose administration At 17 months he had one half of his

METHODS OF STUDY

In order to insure quantitative collections of all urine and feces as well as accurate accounting of the amounts of the special dietary formula consumed by each patient special nurses were assigned to the small metabolic ward where the experimental subjects were kept on specially constructed collection frames The standard semi liquid diet, calculated to be nutritionally adequate in every respect, contained 42 gm of protein 45 gm of fat and 118 gm of carbohydrate in each kilogram The daily allowance adjusted to the caloric needs of the individual subject was given in 3 equal meals served at 7 00 A M 1 00 P M and 7 00 P M

Fasting blood samples for glucose determination and eosinophil cell counts were obtained routinely at 7 00 A M every day or every second day throughout the entire period of study In addition the potassium and inorganic phosphorus of the serum were determined at the end of each major period The 24 hour urine samples were analyzed while fresh for total nitrogen uric acid, creatinine phos phorus chloride, sodium and potassium throughout the entire period of study and for 11 oxycorticosteroids and 17 ketosteroids during the last two days of the control and ACTH periods When successfully collected, stools for each major period were analyzed for N P Cl, Na and K Standard analytical methods were employed for the various substances named The true blood glucose was determined by Nelson s[15] modification of the Shaffer Somogyi[16] method according to which values below 50 mg per 100 ml are regarded as definitely hypoglycemic

In each experiment ACTH was administered intramuscularly in equal doses (either 9 to 10 mg equivalent to Armour standard preparation La 1 A) every 6 hours over a period of 4 days This ex perimental period was preceded by a control or pre period of several days length and was followed by a post period of similar length Sugar tolerance tests were performed in the pre period and again dur ing the latter part of the ACTH period in all cases In this test blood glucose was determined immediately before and 15 minutes 1 hour, 2 hours 3 hours 4 hours and 5 hours after termination of the intra venous infusion of a 25% solution of glucose (0 5 gm glucose per kg of body weight) The ability of the pituitary gland to elaborate or to release ACTH was evaluated by means of the test proposed by Re cant Forsham and Thorn [17] according to which a marked decrease in the eosinophil count 4 hours following the intravenous infusion of epinephrine indicates a normal response The dosage of epinephrine was adjusted to the size of the child R R was given 0 3 mg in 50 ml of saline solution Da R 0 4 in 60 ml De R and J G 0 5 mg in

made in collaboration with Dr E T Bell, suggest a deficiency in the number of alpha cells and a loss of granules in the beta cells of the islets

Case 3

De R, age 5 years was well until 5 months of age when he began to have short episodes characterized by pallor rolling and incoordination of the eyes, crying and tonic convulsions These symptoms were followed by limpness and stupor which lasted from a few minutes to several hours Such episodes were more frequent when his appetite failed as a result of an upper respiratory infection At the age of 18 months he had his first generalized clonic convulsion Thereafter he had from one to four convulsive episodes weekly for several years

When examined by the referring pediatrician in March, 1949 his fasting blood sugar values were found to vary between 18 and 45 mgm % He was placed on a high protein diet but without a satisfactory response He was admitted to the University Hospital for the present study in May 1949 Fasting hypoglycemia was confirmed Other examinations were negative except for strabismus and a moderate degree of mental retardation

Case 4

Da R brother to De R was also admitted to University Hospital in May 1949 at the age of 2½ years because he too had suffered from similar hypoglycemic attacks since the age of 5 months The episodes consisted of a blank stare uncoordinated occular movements irritability pallor, and unconsciousness which occurred most often before breakfast and before supper In March 1949 he like his brother, had been found to have low fasting blood sugar levels

Physical and neurological examinations were normal except for mild strabismus which was accentuated during hypoglycemic attacks

Case 5

R R the 9 month old brother of De R and Da R was admitted with them to the University Hospital for the present study in May 1949 At 2 months of age he had had an upper respiratory infection with anorexia irritability and sweating At 6 months of age he began to have frequent episodes of irritability and sweating but when maintained on 2 hourly feedings he remained symptom free

When the fasting blood sugar was determined it was found to be low Physical and neurological examinations were negative except for slight strabismus Typical manifestations of hypoglycemic reactions were in evidence during episodes

METHODS OF STUDY

In order to insure quantitative collections of all urine and feces as well as accurate accounting of the amounts of the special dietary formula consumed by each patient special nurses were assigned to the small metabolic ward where the experimental subjects were kept on specially constructed collection frames The standard semi liquid diet, calculated to be nutritionally adequate in every respect contained 42 gm of protein 45 gm of fat and 118 gm of carbohydrate in each kilogram The daily allowance adjusted to the caloric needs of the individual subject was given in 3 equal meals served at 7 00 A M , 1 00 P M and 7 00 P M

Fasting blood samples for glucose determination and eosinophil cell counts were obtained routinely at 7 00 A M every day or every second day throughout the entire period of study In addition the potassium and inorganic phosphorus of the serum were determined at the end of each major period The 24 hour urine samples were analyzed while fresh for total nitrogen uric acid creatinine phos phorus chloride sodium and potassium throughout the entire period of study and for 11 oxycorticosteroids and 17 ketosteroids during the last two days of the control and ACTH periods When successfully collected stools for each major period were analyzed for N P Cl Na and K Standard analytical methods were employed for the various substances named The true blood glucose was determined by Nelson s[15] modification of the Shaffer Somogyi[16] method according to which values below 50 mg per 100 ml are regarded as definitely hypoglycemic

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70 ml, the infusion running 1 hour The eosinophil cell counts 4 hours after infusion of epinephrine averaged 31 per c mm, compared to the average initial count of 133 This 78% fall was interpreted as indicating normal capacity on the part of the pituitary to produce ACTH in the 4 cases tested (see Fig 1)

As shown in Fig 2 the epinephrine test for glycogen stores in the liver and for glycogenolytic response (test for von Gierke s glycogen storage disease) was normal in all cases excepting Da R When the

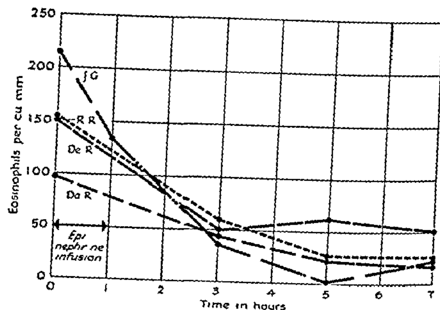


Fig 1 Response of blood eosinophil count to intravenous infusion of epinephrine Marked decrease in count is regarded as an indication of normally functioning adenohypophysis

test was repeated in the case of the latter patient while he was still in a state of fasting hypoglycemia it also was found to be normal Results of a series of other liver function tests were likewise indicative of freedom from hepatic disease All of the series of patients showed hypersensitiveness to insulin The intravenous glucose tolerance test showed increased tolerance in all 5 patients, typical of severe hypoglycemosis

The rise in fasting blood glucose and the fall in blood eosinophil count following a single injection of ACTH indicated a normal adrenal cortical response in each case as exemplified by results in the case of R R shown in Fig 3

RESULTS

The experimental data on the 5 subjects with non Addisonian hypoglycemia included in this study indicate that their responses to ACTH administration are similar in type to those reported for normal adult subjects Severe hypoglycemia and attendant symptoms were completely abolished during the period of intensive hormone administration and for at least a week after its withdrawal (see Figs 4 and 5) The sharp fall and the abnormally prolonged low level of blood sugar in the glucose tolerance curve which represented the

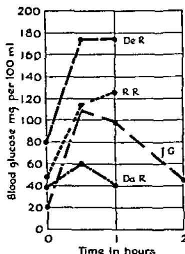


FIG 2 Epinephrine test for glycogen stores in liver and for glycogenolytic function normal in all patients excepting Da R When retested he also showed a normal response

characteristic response of each of the patients during the control period were found to be absent during the period of ACTH administration the curve becoming essentially normal (see Figs 6 and 7) None of the 5 patients showed sugar in the urine at any time during the entire period of study except for the mild glycosuria which occurred at the height of the glucose tolerance test made in the ACTH period in 3 instances Insulin hypersensitivity was likewise counteracted to a certain extent by the ACTH in the cases tested

The eosinophil cells of the blood fell precipitately from the normal range (between 100 and 350 per c mm) to between 0 and 10 per c mm within 4 hours after ACTH was first administered and remained at this low level so long as the hormone was given at 6 hour

intervals While the fasting blood sugar during the post period tended to remain for a number of days at levels intermediate between the hypoglycemic values of the pre period and the normal values of the ACTH period, the eosinophils returned to their original normal counts fairly promptly, usually within a day after withdrawal of the hormone Responses of the blood glucose and eosinophil cell count to ACTH administration are illustrated in Fig 4 which presents data obtained on B G the most severe case in the series Changes in the other cases

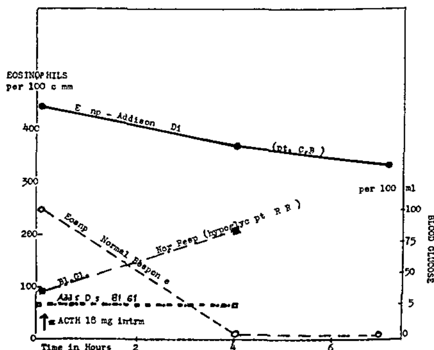


Fig 3 Normal type of fasting blood glucose and eosinophil responses to ACTH shown by patient R R (idiopathic hypoglycemosis) in contrast to negative responses of child (C B) with severe Addison s disease

were very similar to these (Fig 5) The only untoward effects of the ACTH consisted of a transient vasopressor reaction after the injection and a moderate tendency to oliguria during the first day or two of intensive administration These effects appear to be due to contamination with posterior pituitary hormones They were less prominent in lots of the hormone received during the latter part of the period of study

The urinary excretion of 11 oxycorticosteroids and of 17 keto steroids was increased as a result of the ACTH injections by percentages ranging between 75 and 400 At the same time the uric acid

excretion increased 50 to 100% Whereas intensive administration of ACTH induces a negative nitrogen balance in normal adult subjects, a slightly positive balance was maintained in all periods in two of these very young, growing subjects (those with partial pancreatectomy) as long as the full diet was taken However, the magnitude of the positive balance was much less during the period of intensive ACTH ad

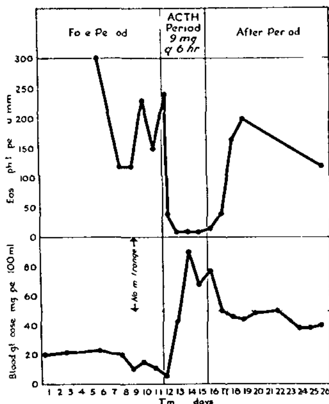


FIG 4 Effects of ACTH on blood eosinophil count and on fasting blood glucose in patient B G

ministration than during the pre and post periods The expected negative nitrogen balance during the ACTH period was found in the other 3 cases The phosphorus balance was likewise slightly positive in all periods for the first 2 patients The size of the positive balance during the ACTH period however was less than that for the fore period and the after period Sodium and chloride showed no significant tendency to increased retention during the ACTH period but showed fairly marked increase in excretion in the post period The comparatively low NaCl content of the diet may account in part for

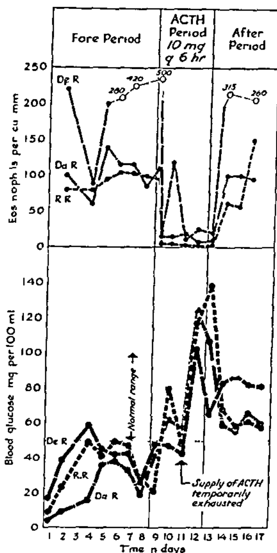


FIG 5 Effects of ACTH on blood eosinophil count and on fasting blood glucose in patients B G and J G

the low degree of retention Potassium showed a small negative balance during the ACTH period but positive balances for the pre period and the post period

There were small but consistent changes in the potassium and inorganic phosphorus of the blood serum of all 5 of the subjects as a result of ACTH administration In every instance both elements fell to lower levels except for a slight rise in the phosphorus in one case The fasting serum K values which were slightly elevated in 3 and near the upper limit of normal in 2 of the cases were decreased from

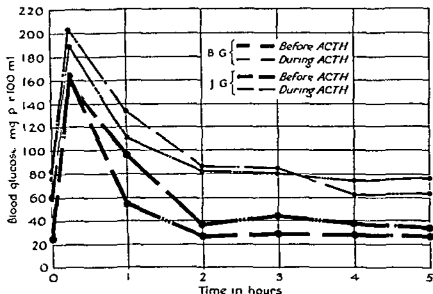


FIG 6 Intravenous glucose tolerance test *before* and *during* ACTH administration in patients B G and J G

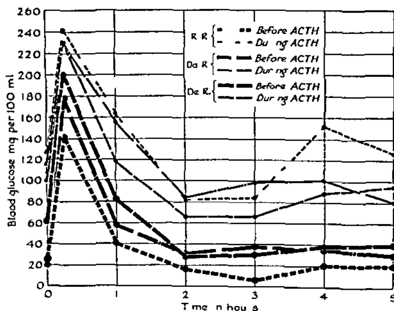


FIG 7 Intravenous glucose tolerance test *before* and *during* ACTH administration in patients R R Da R and De R

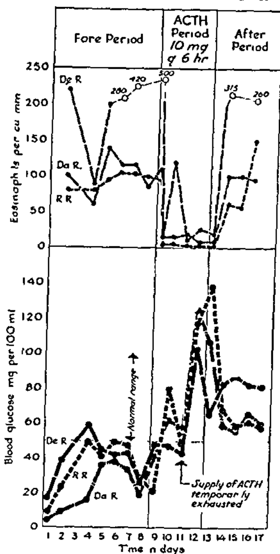


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the serum on the nitrogen phosphorus chloride sodium and pota sium balances on the urinary excretion of uric acid creatinine an adrenal corticosteroids and on the blood eosinophil counts were de termined in 5 young children with non Addisonian (familial) hypo glycemosis The type of response to ACTH was similar in most re spects to that reported for the normal adult

However under the conditions of this study instead of producin a transient state of diabetes mellitus as it does in the normal subjec the ACTH appeared merely to abolish the hypoglycemic tendenc with return of the fasting blood sugar levels and the glucose toleranc curve to normal * While the eosinophil count returned to norm promptly upon withdrawal of ACTH the blood sugar remained abov the threshold for hypoglycemic reactions for some days withou ACTH even in the most severe case in the series In all instance however the original degree of hypoglycemia recurred at varyin periods of time following withdrawal of the ACTH Administration between 18 and 10 mg of ACTH in a single dose every 48 hou sufficed to maintain the most severe case of the series in an essential non hypoglycemic state for more than 6 months after she had bee subjected to intensive ACTH treatment for a few days only No evi dence of refractoriness to the hormone was observed and no signs hypercorticoadrenalism were seen Results of the study sugges therefore that ACTH may prove to be as effective in the control chronic non Addisonian hypoglycemosis in many instances as insuli is in the control of pancreatic diabetes

* Except when the dosage was excessive

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an average of 5 84 meq per liter in the pre period to 5 06 meq per liter at the end of the ACTH period At the same time, the serum P was decreased from an average for the group of 3 03 to 2 70 meq per liter These decreases in serum K and P are interpreted as an indication of increased glycogen deposition during the ACTH period rather than being due to increased excretion The magnitude of the decrease in retention of these two elements appeared to be far too small to influence blood composition

After the fasting blood sugar was allowed to return to pre ACTH levels in the case of B G (Fig 4) the hormone was again given intensively for 2 days thereby restoring the glucose level to normal ACTH was then administered in a single dose of 18 mg once every 2 days for 1 month and between 15 and 10 mg every 2 days thereafter for more than 5 months The fasting blood sugar was determined at the end of each 48 hour period when it was presumably at its lowest level The values so obtained were found to range between 40 and 68 mg per 100 ml throughout the period except for a few days on one occasion when the patient refused a large part of her diet because of an upper respiratory infection Two of the morning values at the latter time were 24 and 16 Her diet which was the unrestricted mixed dietary for a normal child of her age was taken avidly throughout the remainder of the period and her growth and development were satisfactory She learned to walk alone and to talk in the interval No clinical signs of hypoglycemia or of toxic side effects or of refractoriness to the hormone were observed at any time, so long as the hormone was being administered On the contrary the ACTH appeared to be essentially as specific in the routine control of hypoglycemia in this severe case as insulin is in the control of pancreatic diabetes

While it is conceivable that administration of ACTH in large doses over long periods of time might result in permanent damage to the beta cells and thereby cure the hypoglycemosis the small dosages employed in the case of B G did not have this effect to any marked degree as indicated by the fact that hypoglycemia with typical symptoms recurred after 5 months of continuous administration when the hormone was withdrawn for less than a week The experimental production of an antihormone to ACTH has been reported but no evidence of refractoriness to ACTH has been observed in the patients reported here No manifestations of abnormal pigmentation or of Cushing s syndrome have as yet appeared in any of our experimental subjects

SUMMARY

The effects of ACTH on the fasting blood sugar level and glucose tolerance test, on the potassium and inorganic phosphorus content of

21

The Role of the Pituitary Adrenocorticotrophic Hormone (ACTH) and of Adrenal Cortical Steroid Hormones in the Pathological Physiology and Experimental Therapeutics of Clinical Gout

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The adrenal cortical steroids are believed to be implicated both in the inherited susceptibility to gout and in the transition from asymptomatic hyperuricemia to clinical gout Maintenance of secondary sex characteristics and other androgenic functions by an abnormal adrenocortical androgen was postulated when the gouty were found to excrete markedly diminished amounts of urinary 17 ketosteroid in the absence of associated hypogonadism and with an unimpaired ability to convert injected testosterone propionate to urinary 17 ketosteroid That this abnormal adrenocortical androgen might be responsible for the appearance of asymptomatic genetic hyperuricemia in those predisposed by heredity was inferred when normal developmental changes in urate metabolism were compared with the developmental pattern of urate metabolism in individuals with inherited hyperuricemia[1,2,3] Inherited hyperuricemia however is not clinical gout Clinical gout appears to be associated with the presence of a second endocrine disturbance characterized by a disturbed regulation of the rate of secretion of the 11 oxysteroids (11 OS) those adrenal cortical steroids whose metabolic properties resemble those of Compound E

This report will discuss the role of the 11 OS in normal intermediate purine metabolism and in the pathological physiology of

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DISCUSSION

There was no discussion on this paper

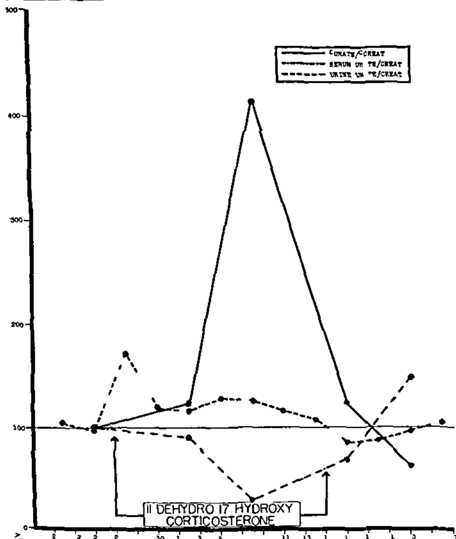


FIG 1 *Effect of prolonged admınıstratıon of Compound E on urate metabolısm* (The ch ınges observed are sımılar to those seen durıng chronıc admınıstra tıon of ACTH These data were obtaıned on a patıent wıth typıcal rheuma toıd polyarthrıtıs studıed by the Mıchael Reese Rheumatoıd Arthrıtıs Re search Group * 300 mg of Compound E were gıven on the fırst day and 100 mg daıly thereafter for the remaınder of the study The Compound E used ın thıs study was made avaılable through the cooperatıon of Dr James Carlısle Medıcal Dırector Merck and Company Rahway N J)

The Rheumato d Arthrıtıs Resea ch G oup n ludes Samuel Soskın M D (Ch aı man) Clarence Cohn M D Roy G ınke M D Henry S Guterman M D Louıs N Katz M D Rachm el Lev ne M D Edwa d F Ro enberg M D Karl Sınger M D Harry F Weısberg M D and W ll am Q Wolfson M D

gout and will attempt to indicate their possible role in therapy The possible significance of these steroids was first suspected by Talbott[4] and his associates who found cyclic changes in electrolyte turnover and in organic metabolism in gout They showed these 'gout cycles' to have a definite temporal relationship to attacks of acute gouty arthritis More recently, it has been found that by endocrine means acute gouty arthritis may be precipitated in a large proportion of interval gout patients[1 5 6 7] and that acute attacks may rapidly be relieved by administration of pituitary adrenocorticotrophic hormone (ACTH) The use of this hormone together with colchicine given concurrently to prevent the return of acute gouty arthritis after ACTH withdrawal has been found a rapid and effective treatment for acute gouty arthritis [8] The administration of ACTH chronically to gout patients can reverse some of the biochemical and tissue pathology of gout Finally a suggestion that the therapeutic action of colchicine in gout may depend upon an ability to release endogenous ACTH [6] warrants critical evaluation particularly because colchicine has been found to afford excellent protection against gout attacks precipitated by ACTH withdrawal

REGULATION OF URATE AND OXYPURINE METABOLISM BY STEROID HORMONES

Forsham, Thorn and their associates[10 11] and Hellman and his co workers[12] have established that 11 oxysteroids are potent regulators of urate metabolism The administration of Compound F [10] Compound E (Fig 1) and to some extent Compound A[11] produces a pattern of changes in urate metabolism which reproduce the changes after ACTH In short term experiments the major effect is an increase in the urine urate/creatinine ratio with little change in the serum urate/creatinine ratio The increase in the ratio of urate clearance/creatinine clearance approximates that of urine urate/creatinine With more prolonged administration either of steroids (Fig 1) or of ACTH a somewhat different pattern occurs There is an initial rise in urine urate/creatinine which may or may not be completely maintained with continued administration Later there is also a significant decrease in the serum urate/creatinine ratio and since it reflects these two changes additively the ratio of urate clearance/creatinine clearance increases markedly When hormone administration is stopped these temporal sequences are reversed The increase in urine urate/creatinine disappears more rapidly upon withdrawal than does the decrease in serum urate/creatinine (see Fig 5) The physiological basis of these temporal differentiations is not clear

The 11 OS are not the sole regulators of urate metabolism Adult

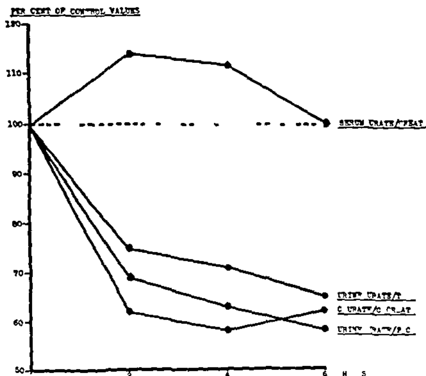


FIG 2 *Average effect of male sex hormones in seven normal children* (The are from a study conducted in cooperation with Dr David Krevsky o Department of Pediatric Research Medical Research Institute Mi Reese Hospital In order to have subjects who were secreting a min amount of endogenous androgen children between 5 and 7 years of age used Four children received 100 mg of testosterone propionate i m and one child received 50 mg Two children each received 100 mg of m androstanediol by mouth

The abbreviations used in the chart are *T C* total creatinine *P C* preformed creatinine)

are the oxypurines xanthine and hypoxanthine Both xanthine hypoxanthine are converted to urate by the enzyme xanthine oxic In man xanthine oxidase has been found only in the liver and production of urate from oxypurine presumably occurs exclusi in this organ[12] Fig 3 illustrates the typical pattern of change oxypurine metabolism which follow the administration of AC Oxypurine changes are the direct reverse of the alterations in u metabolism after ACTH The urine oxypurine creatinine ratio f and the serum oxypurine creatinine ratio rises Together these

men have higher average plasma urate levels than do adult women, and this sex differential obtains in both the normal and gouty groups Children have lower average plasma urate levels than do either normal men or women Children moreover show no sex differential in plasma urate levels The ratios of urine urate/creatinine and urate clearance/creatinine clearance are both appreciably higher in children than in adults With late childhood and puberty, each of these values changes toward its adult level Because these developmental changes are all more marked in boys than in girls they ultimately lead to the establishment of the normal adult sex differential in plasma urate and in the ratio of urate clearance/creatinine clearance [1 3]

From the association of these developmental changes with puberty and from their greater intensity in boys it was considered that they probably reflected the onset of androgen secretion by both the adrenal and testis in boys and by the adrenal in girls Fig 2 shows that similar changes may be produced by administering potent androgens to young children The resulting changes in urate metabolism are directly opposite to those produced by ACTH More recent and still incomplete observations suggest that there is no necessary connection between the ability of a steroid to produce androgenic effects on *urate metabolism and the degree of masculinization which it induces*

The carriers of genetic hyperuricemia in gouty families also have normal plasma urate levels until puberty if male and until the menopause if female The exaggerated increases in urate level occurring in carriers at puberty and menopause respectively cannot be explained as due to an excess of normal androgen Not only is there evidence from the study of 17 ketosteroid excretion that the gouty secrete less normal androgen than do the non gouty but clinically hyper androgenism is not observed in gouty men and virilism is not a feature of gout in women The exaggerated developmental changes in urate metabolism in those inheriting asymptomatic hyperuricemia therefore are believed to represent the influence of an abnormal androgen This androgen is presumably of adrenocortical origin since hyperuricemia may be inherited by either sex [1 3]

From such considerations urate metabolism may be viewed as a metabolic process regulated by the opposing influence of 11 OS and of androgens (normal or abnormal) Urate metabolism in the child resembles that of the adult during chronic ACTH administration not because the child secretes abnormally large amounts of 11 OS but because his androgen *secretion is very small One may also see a child*hood like pattern of urate metabolism in certain cases of Cushing s syndrome or acromegaly In such a high 11 OS/androgen ratio results from high rates of 11 OS secretion Table 1 summarizes these observations

The *immediate precursors of urate in intermediate* metabolism

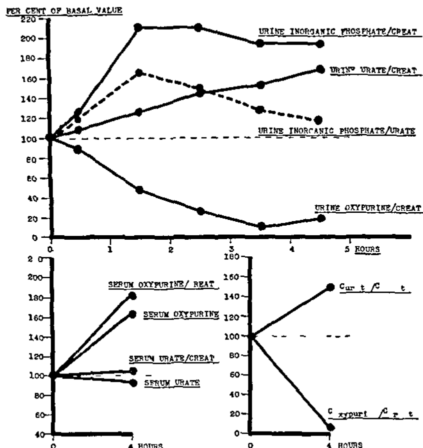


FIG 3 *Average course of changes in urate and oxypurine metabolism and in inorganic phosphate excretion following 33 mgm of aqueous ACTH in one non gouty and in two gouty subjects* (Urate was estimated colorimetrically by a conventional Folin Benedict arsenophosphotungstate method with urea cyanide color intensification Oxypurine was estimated enzymatically by the xanthine oxidase method of Wolfson Cohn Levine and Kadota in which the amount of urate appearing after samples are treated with enzyme is considered to represent the oxypurine [8])

tendency for acute gouty arthritis to follow the induction of relative 11 oxysteroid lack Hellman and Robinson Conn Block and Louis[6] produced acute 11 OS lack by first administering ACTH to interval gout patients and then withdrawing the hormone A recognizable attack of acute gouty arthritis generally began within 96 hours after ACTH withdrawal Occasionally as in Fig 4 an attack may follow even a single moderate dose of ACTH and the onset of the attack

creatinine clearance These alterations are sensitive indicators of ACTH response but are variable, at least partly because of intrinsic difficulty in the method of oxypurine determination As yet, the effects of androgen on oxypurine metabolism have not been studied

While it is not yet known whether hyperuricemia is directly responsible for any of the manifestations of gout other than the tophus clinical gout seems more often to appear when antecedent elevations in serum urate have been prolonged and large [1] Hence, by evoking hyperuricemia, the abnormal androgen of gout may govern the basic susceptibility to the disease Little additional is known of the intimate mechanism by which the endocrines affect purine metabolism The

Table 1

REGULATION OF URATE METABOLISM BY STEROID HORMONES

11 OXYSTEROID / ANDROGEN	High	Low
Occurrence	Normal Children Adults Given ACTH Hypercorticoidism	Children Given Androgen Gout* Adrenogenital Syndrome†
Serum Urate/Creatinine	Low	High
Urine Urate/Creatinine	High	Low
Urate Clearance / Creatinine Clearance	High	Low

* In gout there is believed to be a low 11 OS/androgen ratio which results not from an excess of normal androgen but from an abnormal androgen which is not a precursor of urinary 17 ketosteroid

† Data from a limited number of cases

available information permits no reliable decision as to whether ACTH increases or decreases the rate of urate production Knowledge of the ACTH induced changes in oxypurine metabolism add no additional clarification The major difficulty arises from the loss of an unknown, but variable amount of urate from the body via the gastrointestinal tract and liver Purely chemical methods are unsatisfactory for the study of this problem but isotope methods should ultimately lead to its solution

A DEFICIENT RESPONSE TO 11 OXYSTEROID LACK IN CLINICAL GOUT

Hormonal Induction and Relief of Acute Gouty Arthritis

The second endocrine disturbance in clinical gout is a deficient response to 11 oxysteroid lack A clinical sign of this disturbance is the

of their attack within a few days. We have observed a similar sequence of relief and recurrence to follow a single 50 ml dose of aqueous adrenal cortical extract (Wilson) given intravenously. Apparently, withdrawal of 11 OS or ACTH tends to induce an attack irrespective of the clinical condition of the patient when administration originally was begun.

Defective "Rebound" Counter regulation in Clinical Gout

In all subjects ACTH withdrawal is followed by a period of relative 11 OS lack which is more or less severe depending in part on the time and total dosage of previous ACTH administration. The administration of exogenous ACTH by raising the circulating 11 OS level inhibits the rate at which the pituitary releases ACTH. The degree to which release of endogenous ACTH is inhibited has been shown by Sayers and Sayers[14] to be a direct function of the level to which 11 OS have been raised. Relative 11 OS lack following ACTH withdrawal appears to represent the tendency of a steroid induced inhibition of endogenous ACTH release to persist until corrected by adequate stimulation.

Conn and his associates[1, 16] have particularly interested themselves in the counter regulatory phenomena occurring after ACTH withdrawal. In normal adults the period of 11 OS lack which follows hormone withdrawal is terminated by a short burst of "rebound"* 11 OS excess as the pituitary finally increases its rate of ACTH release and overshoots the amount required to restore 11 OS level to normal. After this or occasionally after a number of periods of alternating "rebound" and 11 OS lack, pituitary adrenal regulation once again becomes stable, usually at about the original level.

In gout patients "rebound" appears defective.[5, 7] Fig 5 shows an example of brisk "normal" rebound which contrasts with the absence of "rebound" in the gout patients illustrated by Figs 4 and 13. In the gouty even if ACTH withdrawal does not precipitate acute gouty arthritis, "rebound" still may be absent. In such cases as Hellman observed, the 11 OS lack after ACTH withdrawal tends to be corrected by a slow return of metabolic processes to normal rather than by the efficient counter regulation which normal "rebound" implies.

The Adrenal Cortex and Spontaneous Gout Attacks: Defective Response of the Gouty to Acute Gouty Arthritis

In their studies of the "gouty cycle" Talbott and his associates found that during one phase of these cycles there occurred a char

* Use of the term "rebound" should be restricted to observations in which there is a rapid change from a state of asymptomatic 11 OS lack to an 11 OS level above normal or above that obtaining before hormone administration. It is not properly applied when 11 OS levels tend to return from low to merely normal values or to instances in which a gout patient responds promptly to the stress of an attack by increasing his 11 OS output.

may sometimes be deferred for more than 96 hours after hormone withdrawal

Either a spontaneous gout attack or one provoked by ACTH withdrawal may rapidly be relieved by adequate amounts of ACTH However when the hormone is withdrawn a state of 11 OS lack is once again induced and many patients will experience a recurrence

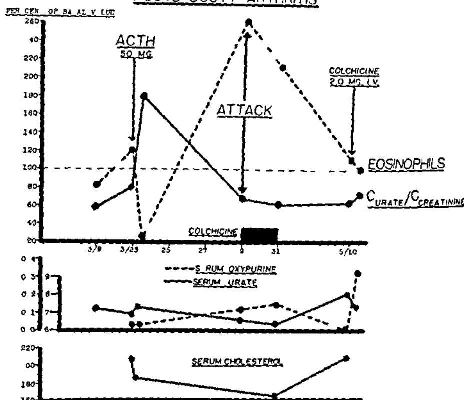


FIG 4 *Deficient response to ACTH withdrawal acute gouty arthritis* (The data are from P P a patient with pretophaceous gout who has had only one spontaneous attack of gouty arthritis Induction of this attack was accidental since we believed at that time that acute gouty arthritis could not be induced with a single 50 mg dose of ACTH Note the persistent eosinophilia and decrease in urate/creatinine clearance ratio which showed 11 oxysteroid lack to be present 6 days after the test dose of ACTH Colchicine relieved this attack promptly but did not appear to increase 11 oxysteroid output

At the far right the effects of 2.0 mg of colchicine given intravenously are shown for comparison These are qualitatively similar to those of ACTH, but quantitatively are far less marked than those produced by 50 mg of ACTH We are indebted to Dr Eric C Kast for his cooperation in referring this patient to us)

acteristic diuresis in which sodium and chloride were lost in excess of water, as in a temporary adrenocortical insufficiency [4] This diuresis tended to follow a fall in external barometric pressure Not every such diuretic phase was followed by an attack but when attacks did occur, they followed this diuresis These prodromal changes in electrolyte turnover suggested prodromal mineralocorticoid lack while certain other findings were consistent with a simultaneous deficiency of 11 OS The long known prodromal decrease in urate output has recently been confirmed by Loffler and Koller[18] who also showed a prodromal decrease in urate clearance An interesting old study by Futcher[19] reports a prodromal decrease in phosphate excretion

Such metabolic observations suggest that spontaneous gout attacks like those which follow ACTH withdrawal are preceded by a period of relative 11 OS lack This relative 11 OS lack may originate in different ways Many known incitants of acute gouty arthritis such as surgical operations appear to increase 11 OS utilization Most attacks however follow no known incitant Study of serum cholesterol variations has provided a clue as to the possible origin of certain spontaneous attacks Conn and Vogel[1] have recently suggested a relation of acute changes in serum cholesterol level to the rate of adrenal 11 OS formation as do observations summarized elsewhere [13] In a few spontaneous gout attacks we have been fortunate enough to obtain blood samples within 24 hours of the onset and have observed maximal serum cholesterol concentrations to obtain at that time This has suggested that withdrawal of endogenous ACTH may be responsible for prodromal 11 OS lack in certain spontaneous attacks In general therefore spontaneous attacks are apparently precipitated by persistent relative 11 OS lack just as are attacks induced by ACTH withdrawal

During the developing attack particularly when it is unusually severe or resistant to therapy metabolic changes indicative of continuing 11 OS lack may occasionally be observed More frequently, it is necessary to infer the existence of relative 11 OS lack from absence of evidences of super normal 11 OS production despite fever and incapacitating acute inflammatory arthritis Fig 6 shows the absence of significant eosinopenia (generally the most sensitive indirect index of increased 11 OS output) lymphopenia or polymorphonuclear leukocytosis during the average attack Figs 7 8 and 9 show that while changes in oxypurine metabolism suggest some slight

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ment The data agree with those of Conn and his associates[15 16] in showing the effects of rebound on urate metabolism to be particularly marked We wish to thank Dr William Saphir and Dr Sidney O Levinson for referring this patient for study)

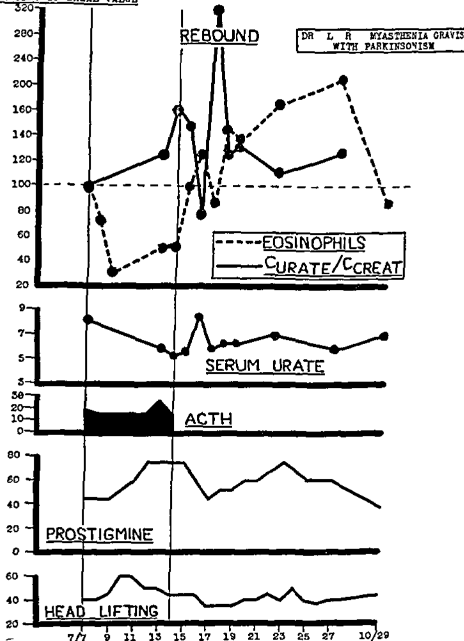


FIG 5 *Normal 'rebound' phenomenon following ACTH withdrawal in a patient with myasthenia gravis and hyperuricemia of undetermined origin* (The data are from Dr L R The total amount of ACTH given during this study is now known to have been inadequate and therefore probably explains the failure to obtain a remission in this patient's myasthenia However the patient's serum urate has never returned to values as high as those observed before treat

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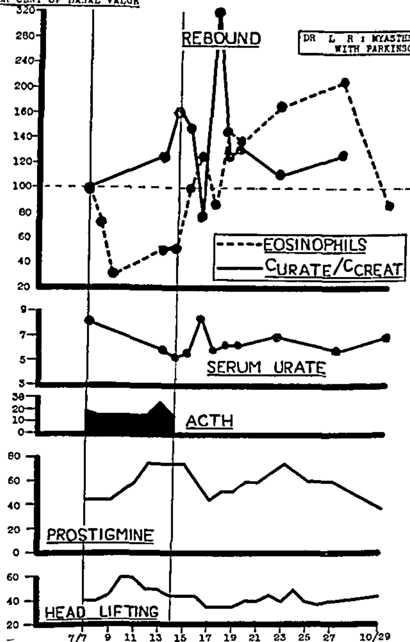


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lease rather than to inability of the adrenal cortex to respond to stimulation

Adrenal Cortical Responsiveness and Hypothalamo pituitary Responsiveness in Gout Patients

Both the therapeutic effect of ACTH in acute gouty arthritis and the data of Figs 6 through 9 show that the adrenal cortex is not absolutely unresponsive in gout Fig 10 summarizes the responses of gout

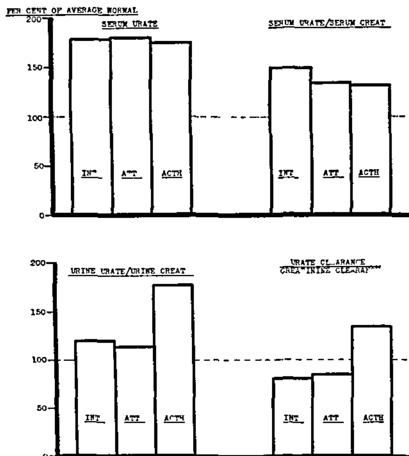


Fig 7 *Deficient response of gout patients to acute gouty arthritis absence of alterations in urate metabolism during attacks* (Average data from the patients of Fig 6 The attacks studied were largely episodes which showed little tendency to end spontaneously and therefore do not show the increased urate excretion presumably due to increased 11 OS output which is seen during spontaneous recovery from an attack)

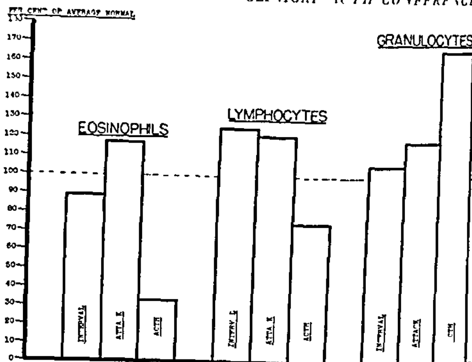


Fig 6 *Deficient response of gout patients to acute gouty arthritis absence of eosinopenia lymphopenia and granulocytosis during acute attacks* (The data compare findings in 10 patients during interval gout during attacks and following the administration of 50 mg of ACTH during an attack Basal values for differential leukocyte patterns confirm other observations which suggest 11 oxysteroid production to be normal during interval gout, with little change from the basal levels occurring during attacks From the changes occurring after the administration of ACTH it may be inferred that although adrenal cortical responsiveness is somewhat reduced on the average the adrenal cortex responds sufficiently well to indicate the presence of increased amounts of ACTH Failure of hematological findings to change during attacks must therefore indicate that extra ACTH was not released Similar observations on a larger group of gout patients who were not studied during ACTH administration have been reported elsewhere [9])

increase in 11 OS output over levels obtaining during interval gout there is no similar suggestion from urate metabolism urine inorganic phosphate/creatinine ratios and 17 ketosteroid excretion The data on response to ACTH during acute attacks which is included in Figs 6 through 9 show that during attacks the adrenal cortex responds to stimulation by ACTH The failure of gout patients to increase 11 OS output in response to acute gouty arthritis appears more referable to failure of the pituitary to increase its rate of ACTH re

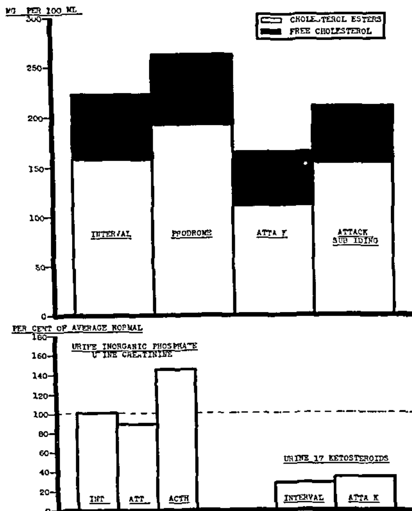


FIG 3 *Deficient response of gout patients to acute gouty arthritis changes in serum cholesterol in urine inorganic phosphate and in urine 17 ketosteroid excretion during acute attacks* (Data on inorganic phosphate excretion were obtained in the patient of the preceding 3 figures 17 Ketosteroid excretion was studied in 19 patients and serum cholesterol in 35 patients Because normal standards for urine inorganic phosphate/creatinine were not available the level obtaining in interval gout has been given as the 100% value As noted elsewhere [2] 17 ketosteroid values as low as those shown will be obtained in gout patients only if the method used involves a preliminary separation of the neutral ketonic steroids with the Girard T reagent The prodromal rise in serum cholesterol is a preliminary finding since only a few patients have been studied in the prodromal period

The decrease in serum cholesterol during acute gouty arthritis is difficult to interpret The observations of Conn and Vogel[17] suggest that such acute

patients to 50 mg of ACTH in short term studies The average eosinopenia and lymphopenia approximate changes found in a normal adult after 25 mg of ACTH, while the metabolic responses are somewhat below the standard changes induced in normal subjects by 25 mg of

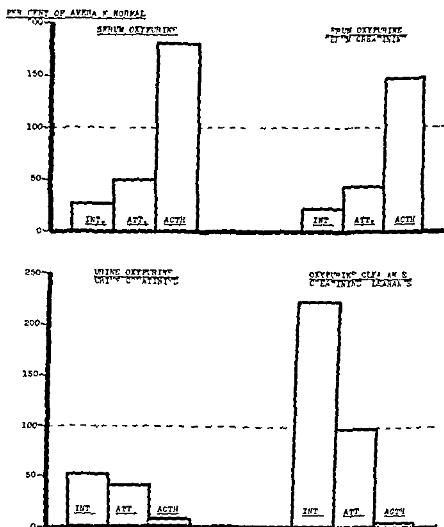


Fig 8 *Deficient response of gout patients to acute gouty arthritis alterations in oxypurine metabolism during acute attacks* (Average data from the patients of Fig 6 Note the low basal serum oxypurine level which appears to be characteristic of interval gout The changes observed in oxypurine metabolism suggest that a small extra amount of 11 oxysteroid may be released during the attacks Alterations in oxypurine metabolism appear to be a sensitive but irregular index of adrenal cortical response The irregularity is at least in part due to difficulty in measuring the small amounts present either in serum or in urine)

withdrawal Clinically, this defect is indicated by the regularity with which induced 11 OS lack is permitted to persist and to precipitate acute gouty arthritis Even the stress of an acute attack in most cases

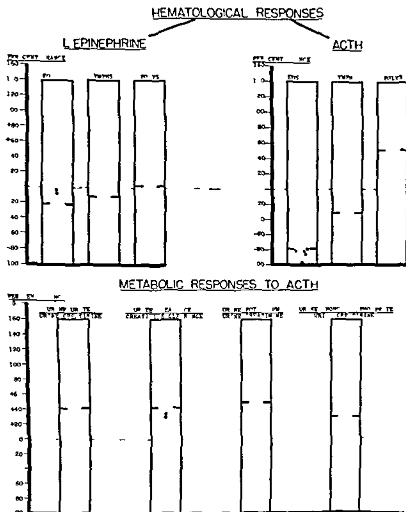


Fig 10 *Hematological and metabolic effects of ACTH and of L-epinephrine in gout* (The heavy horizontal lines indicate median responses The ACTH data show the 4 hour responses to 50 mg doses of ACTH in gout patients to whom no ACTH previously had been given The l epinephrine data show the 4 hour responses to 0 2 mg in fully colchicinized patients who were known to be responsive to ACTH Five of the patients tested with l epinephrine had been found responsive to initial doses of ACTH the remaining two had been primed by ACTH administration within a few days of being tested with l-epinephrine)

ACTH[10] Thus the effect of 50 mg of ACTH upon a theoretical average gouty adrenal seems slightly less than that ordinarily produced in normal subjects by a dose half as large The variability in response is large A few patients generally those whose gout was well controlled had entirely normal responses Two patients were found to be entirely unresponsive to 25 mg of ACTH in initial tests The decreased responsiveness of the gouty adrenal is not that of a gland already stimulated to maximal functional capacity for none of the functional indices of Figs 6 through 9 show indications of adrenal cortical hyper activity either in interval gout or during the attack Detailed studies presented below on one of the patients found absolutely unresponsive to initial doses of ACTH suggested his adrenal unresponsiveness to arise from chronic understimulation

From Hume s studies the release of additional ACTH during stress is now known to depend upon the activation of an anterior hypothalamic secretory center possibly located in the large celled portion of the paraventricular nuclei[21] This center secretes a neuro humoral substance which releases ACTH from the anterior pituitary Injury to the center abolishes the eosinopenic response to physical stress or to 1 epinephrine Administration of standard small doses of 1 epinephrine may be used to test the integrity of the hypothalamo-pituitary system controlling ACTH release providing the adrenal cortex is responsive to ACTH

In cooperation with Robinson studies of responses to 1 epinephrine have been performed on colchicinized and on uncolchicinized gout patients Fig 10 summarizes our results in 6 colchicinized gout patients which do not differ significantly from those obtained by Robinson in uncolchicinized patients In both groups the median response to 1 epinephrine is distinctly subnormal and individual results vary from absolute unresponsiveness to an occasional normal response

Nature and Locus of Deficient 11 Oxysteroid Regulation in Gout

An interval gout patient ordinarily exhibits no evidence either of adrenal cortical hyperfunction or hypofunction However he exhibits impaired ability to meet a state of relative 11 oxysteroid lack by promptly increasing 11 oxysteroid output Metabolically this disturbance is reflected in his deficiency in rebound after ACTH

changes indicate an increased rate of 11 oxysteroid formation as do other studies[13] However most indices of adrenal function give little evidence of an increased 11 oxysteroid output during acute gouty arthritis It is possible that the adrenal cortex is producing steroids which require withdrawal of serum cholesterol but which are not functional 11 oxysteroids)

Table 2

OBSERVATIONS INDICATING POSSIBLE DIFFERENCES IN PITUITARY ADRENAL REGULATION AND FUNCTION IN GOUT AND IN RHEUMATOID ARTHRITIS

	Gout	*Rheumatoid Arthritis*
Withdrawal of ACTH	Incites attacks	Induces relaps
Administration of ACTH	Relieves attacks	Temporary remission
Fasting Ketosis High Fat Diet	Incites attacks	Temporary remission
Operations and Sudden Stress	Incites attacks	Temporary remission
Colchicine*	Relieves attacks	Little effect
Hepatitis*	No effect	Temporary remission
Pregnancy	[illegible]	Temporary remission

The ineffectiveness of hepatitis in gout and of colchicine in rheumatoid arthritis[2] suggest that neither agent acts solely by increasing 11 OS output

Fig 11 summarizes the results of ACTH colchicine treatment in the first 18 attacks A majority were effectively terminated within 12 hours by a single 50 mg dose of ACTH and at least half were over within 6 hours after the first dose of hormone was given An initial dose smaller than 50 mg appears inadvisable because of the number of individuals in the gout groups whose adrenals are somewhat sub normally responsive when initially stimulated In 5 attacks a second 50 mg dose was required 6 to 12 hours after the initial dose while a third dose of 50 mg was required in a single attack With one excep tion no attack lasted more than 24 hours after ACTH administra tion was begun

Most patients experience little change in symptoms for 1 or 2 hours after ACTH is given Pain then usually begins to subside and the recession of discomfort is frequently so rapid that patients com ment with surprise upon their minute to minute improvement In that minority of patients who require more than one dose of ACTH this rapid symptomatic improvement may be deferred until after the second dose or until after a third dose of ACTH Except when at tacks are treated very soon after their onset some residual soreness or feeling of tenseness usually remains in the previously involved joint even when maximal improvement has been attained and palpatory tenderness has been reduced to less than Grade 1 These abnormal sensations disappear slowly but are generally not sufficiently trouble some to keep the patient from walking considerable distances Quite

produces no early evidence of compensatory adrenal cortical hyperfunction

This inability of the gouty to cope with relative 11 OS lack does not arise from adrenal cortical unresponsiveness to ACTH Average response to ACTH is to be sure somewhat subnormal but the impairment is not sufficient to prevent a good therapeutic response when extra exogenous ACTH is given in relatively small amounts The common defect appears to be failure to release extra ACTH when the normally adequate *stimulus of 11 OS lack is presented* Such a disturbance might arise either from a disturbance in the pituitary itself or in its anterior hypothalamic control Hume has found that animals with lesions of the anterior hypothalamic neurohumoral center may exhibit little evidence of ACTH lack under basal conditions and yet may be entirely unresponsive to stress This pattern exactly reproduces the disturbance commonly found in patients with clinical gout Preliminary data obtained by a technique which offers some promise of directly testing the integrity of the anterior hypothalamic center has suggested that a defect in this center may exist in those gout patients who do not release ACTH when given l epinephrine

Possible Differences in Pituitary-adrenal Regulation in Gout and Rheumatoid Arthritis

In both of the chronic inflammatory rheumatic diseases gout and rheumatoid arthritis the adrenal cortex fails to provide the extra amount of 11 OS necessary to halt the disease promptly One is probably not justified in concluding from this superficial similarity that an identical defect in pituitary adrenal regulation occurs in these diseases Table 2 summarizes observations which suggest definite differences to exist in the function and regulation of the hypothalamo pituitary adrenal system in gout and in rheumatoid arthritis

RAPID TREATMENT OF ACUTE GOUTY ARTHRITIS BY THE CONCURRENT ADMINISTRATION OF *ACTH AND COLCHICINE*

The tendency of gout attacks relieved by ACTH to return after hormone withdrawal obviously limits the use of ACTH as the sole therapeutic agent for acute gouty arthritis Fortunately the concurrent use of colchicine appears to overcome this tendency and to permit full advantage to be taken of the rapid termination of an attack which ACTH can produce Moreover, the amounts of ACTH ordinarily required for this combined treatment of acute gouty arthritis are small enough to be practicable even under present conditions of limited production

peated daily until appearance of the first gastro intestinal symptoms indicated the presence of full colchicinization Both oral and intravenous* routes have been used for colchicinization Because somewhat more colchicine may be tolerated before diarrhoea if it is given intravenously this route has been preferred in treating attacks which previously had failed to respond to a course of oral colchicine Administration has been withheld for 24 hours as soon as colchicine diarrhoea was noted and then resumed with a dose of 1 5 mg /day If diarrhoea recurred a further downward adjustment of dosage was made However once the maximum dose tolerated daily has been determined this amount has been given each day for at least 2 weeks or until all residual soreness has been relieved Maintenance colchicinization has often been continued for one or more years without toxicity or tolerance developing

No patient who has received combined ACTH colchicine treatment for acute gouty arthritis has had even a minor recurrence of the attack within one month of treatment The concurrent administration of ACTH and colchicine appears to be the most rapid and effective treatment now available for acute gouty arthritis

EVALUATION OF AN HYPOTHESIS THAT THE THERAPEUTIC EFFECT OF COLCHICINE IN GOUT IS DUE TO THE RELEASE OF ENDOGENOUS ADRENOCORTICOTROPHIN

Hellman[5] speculated that the action of colchicine in gout might be due to release of ACTH from the patient s pituitary because of observations by Selye and Leblond in which toxic doses of colchicine were shown to release ACTH in animals Actually the dose levels used in these experiments were far beyond those ever employed in the treatment of gout Such large doses do elicit the alarm reaction but this is a non specific response which may be evoked by many toxic agents with no particular value for the treatment of gout

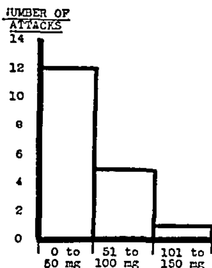
There are clinical objections to an ACTH release hypothesis If it were correct, colchicine should be very useful in the treatment of rheumatoid arthritis since this disease is dramatically relieved by ACTH Lockie [24] however found colchicine to have little value in rheumatoid arthritis Moreover if colchicine released ACTH in significant amounts it should have been possible regularly to precipitate

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* Colchicin for intra venous administration was prepared in 1 0 ml ampules containing 0 5 mg of colchicine in aqueous solution These were made available through the kind cooperation of Dr E A Sharp of the Department of Clinical Research Parke Davis and Company Detroit

often, patients have noted the disappearance of pain from joints which they previously had not recognized as involved

Changes in emotional state have been particularly interesting There is present during acute gouty arthritis an unpleasant mental state which when fully developed appears as a characteristic irritable "touchiness" tenseness and depression Our patients and their families uniformly agree that this disturbance in mood appears well before the attack and is not caused by the pain of the attack Its onset



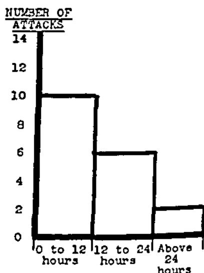


FIG 11 *Results of ACTH colchicine therapy in acute gouty arthritis* (No patient receiving ACTH colchicine therapy required retreatment within one month)

occasionally permits the patient to predict the imminence of an attack Following ACTH this mood changes markedly and is replaced by the characteristic extroverted joviality of interval gout The change may precede accompany or occur somewhat later than the period of rapid symptomatic improvement in the involved joints The shift in mood often is appreciated by the patients almost as much as relief from the pain of the attack itself

Administration of colchicine has been begun simultaneously with ACTH when metabolic data were not needed or 4 hours after the last dose of ACTH when metabolic studies were in progress On the first day 2 0 mg of colchicine has been given and this dose has been re

in 24 hour urinary constituents when therapeutic amounts of colchicine were given. Their results show no appreciable ACTH release by colchicine and so dispose of a theoretical possibility that colchicine might cause a slow but persistent release of ACTH from the pituitary.

Certain related variants of the ACTH release hypothesis have also been considered. Because Busquet[8] found colchicine to potentiate both inhibitory and excitatory circulatory responses to adrenalin, an unsuccessful attempt has been made to show that colchicine restored ACTH release after l-epinephrine to normal in gout patients. The possible effect of colchicine in restoring "rebound" after ACTH withdrawal has been studied. Fig. 13 shows one of these observations. All uniformly indicated no detectable improvement in the "rebound" defect to follow colchicine administration. Fig. 14, finally, is of particular interest since it indicates that the time at which ACTH release after colchicine occurs has no necessary relation to the time at which symptomatic relief occurs.

The information now available suggests that therapeutic doses of colchicine may release small amounts of ACTH in man, but that this action is evanescent, quantitatively unimportant, and incapable of explaining the therapeutic action of colchicine. We do not yet know how colchicine relieves or prevents acute gouty arthritis.

CASE REPORT: SOME EFFECTS OF CHRONIC ACTH ADMINISTRATION IN A PATIENT WITH TOPHACEOUS GOUT, FALL HAY FEVER, AND HYPERSENSITIVITY TO COLCHICINE

Three gout patients have been studied during the chronic administration of ACTH. The findings were sufficiently instructive in one of these patients to warrant detailed review.

Mr. M. K. was first seen during the fall of 1948 during a severe polycyclic polyarticular attack of gouty arthritis which for some time resisted all therapeutic efforts. The difficulty appeared largely to arise from his marked hypersensitivity to colchicine. When tested with oral colchicine he never tolerated more than 0.38 mg./day for more than a few days without developing bloody diarrhoea. During one period, his chronic oral tolerance was as low as 0.10 mg./day.* Daily intravenous administration of colchicine was begun early in January 1949. It was found possible to give him slightly larger amounts of colchicine

* The average daily oral dose of colchicine tolerated chronically by patients in our series has generally been 1.3 to 2.6 mg./day. An occasional patient has had a slightly lower tolerance. The relation between the total dose necessary to achieve colchicinization and the maintenance dose suggests that between 10% and 20% of the colchicine in the body is excreted or metabolized daily. In general, both the colchicinizing dose and the maintenance dose appear more variable than the comparable values for digitalization and maintenance of digitalization.

acute gouty arthritis by first giving colchicine to an interval gout patient and then withdrawing it. This experiment has regularly proven unsuccessful in our hands.

Nevertheless, because of the marked prophylactic potency of colchicine against ACTH withdrawal attacks of acute gouty arthritis, experimental studies of the release of ACTH in man by therapeutic doses of colchicine were undertaken by Robinson and his associates

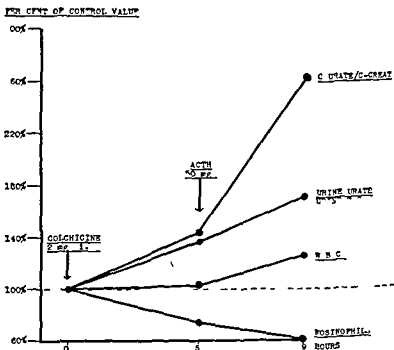
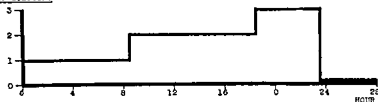


FIG. 12. *Although colchicine appears to release ACTH in man, the amount of ACTH released appears to be quantitatively insignificant.* (The data shown are from P. G., a normal adult. Similar observations in P. P., a gout patient, are shown in Fig. 4.)

and by our group. We found that if ACTH release were judged by metabolic and hematological changes, there did appear evidence 4 to 6 hours after 1.0 to 2.0 mg. of colchicine had been given intravenously that a small amount of ACTH had been released. Fig. 12 shows an experiment in which changes produced by colchicine may be compared with those produced by 50 mg. of ACTH given later. In this experiment, and in all others in our study, the amount of ACTH released appeared to be relatively slight (see also Figs. 4, 13, and 14).

Robinson and associates[7] employed a somewhat different technique. They evaluated ACTH release by the magnitude of changes



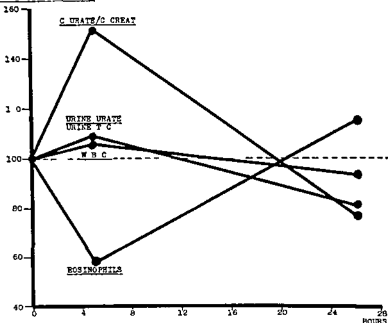


FIG 14 *The time at which colchicine releases ACTH may not coincide with the time at which it produces relief of symptoms* (Patient M K was permitted to accumulate a colchicine deficit of about 2 5 mg by omission of his daily ration for some days A mild Grade 1 articular attack began on the morning of the experiment 2 0 mg of colchicine were given intravenously at Hour 0 Nevertheless the attack steadily became more severe until at Hour 19 he found it necessary to use a cane to get about He experienced sudden relief at Hour 23 and rapidly became pain free Similar delays have been noted previously in this patient between doses of i v colchicine and the onset of diarrhoea)

by this route and his attack soon ended He has been maintained on intravenous colchicine given daily or once every two days for the past 10 months During this time he has had only 2 or 3 minor attacks and has worked continuously Attempts to transfer him to oral colchicine led promptly to bloody diarrhoea when a dose identical with that tolerated intravenously was given If the daily oral dose was reduced

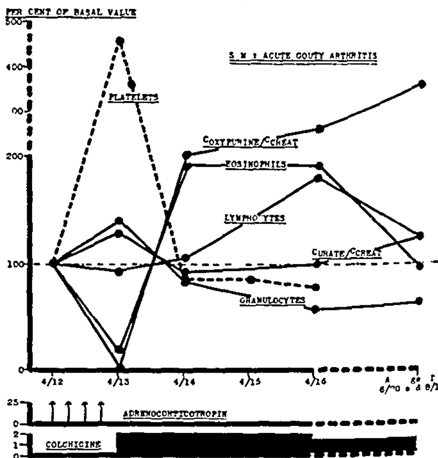


FIG 13 *Colchicine neither restores normal "rebound" after ACTH withdrawal nor produces evidence of increased 11 oxysteroid production even though it successfully prevents the return of acute arthritis* (The data are from S M a patient with acute gouty arthritis Colchicine was begun 4 hours after the last dose of ACTH and continued as a dose level of 2 0 mg /day until the appearance of diarrhoea on 4/16 It was then omitted for 24 hours and resumed at a level of 1 5 mg /day There was steady improvement Note the absence of evidence of "rebound" at the time of full colchicinization on 4/16 Similar data have been obtained in a number of other attacks in other patients

The marked increase in platelet during the administration of ACTH represents a previously unreported finding Through the cooperation of Dr Karl Singer this finding was checked within a few hours of the time it was originally noted and was confirmed by both direct and indirect platelet counts Since other investigators have reported ACTH not to alter platelet levels this finding may represent an individual variation in response

We are indebted to Dr John Marlowe for his cooperation in referring this patient for study and for treatment and to Dr Karl Singer for assistance in platelet counts)

fourth day On a second occasion also shown in Fig 15 this experiment was repeated with 50 mg doses of ACTH given on 4 successive days The results were similar A test with 1 epinephrine before his

Fig 16 *Possible hypopituitarism with respect to ACTH in patient M K* (The data show almost complete unresponsiveness to an initial 25 mg dose of ACTH with some improvement after 4 days of administration and markedly subnormal responsiveness to an initial 50 mg dose of ACTH again with some improvement upon repetition Even after the adrenal had been primed to normal responsiveness (see Figs 17 and 18) l-epinephrine did not release ACTH

Initial unresponsiveness with gradually improving response has been shown by Forsham and associates[10] to be a characteristic of the adrenal cortex of panhypopituitarism and is believed to indicate an atrophic adrenal cortex which has been chronically understimulated by ACTH This finding therefore has been assumed to show chronic undersecretion of ACTH in patient M K Since other data indicated relatively normal secretion of other pituitary hormones the undersecretion of ACTH appeared to be a elective disturbance justifying the diagnosis given above)

to a sub diarrhoeal level ominous prodromata of an attack appeared

Fig 15 summarizes Mr M K 's basic clinical and laboratory findings Despite his tophaceous gout and history of acute glomerulonephritis, his renal function remains virtually intact His findings typify as pure a form of the metabolic disturbance of gout as we yet have encountered His average serum urate creatinine ratio is 10 5 an unusually high value which is almost double the average normal In addition he illustrates well the endocrine paradox which led us to postulate an abnormal androgen in gout [1] He has no signs of clinical hypogonadism normal muscle mass (creatinine coefficient) consider



Fig 15 Mr M K Tophaceous gout obesity hay fever (?) hypopituitarism with respect to ACTH

ing his degree of obesity no creatinuria and a sperm count of 100 000,000 Nevertheless his urinary 17 ketosteroid output has averaged only 1 66 mg /day a level ordinarily seen only in thyroid pituitary or adrenal failure

From the data of Fig 15 one may infer that this patient s pituitary must secrete approximately normal amounts of growth hormone thyrotrophic hormone and follicle stimulating hormone Opportunity to study his pituitary adrenal regulation was provided by 2 mild attacks of acute gouty arthritis which occurred early in 1949 On the first occasions he received 25 mg of ACTH on each of 4 successive days Fig 16 shows the absence of any detectable response on the first day with gradual improvement to a markedly subnormal response on the

certain other metabolic functions He received a total of 900 mg of ACTH in the first 8 days of the study By the end of this time the tophi on his ears had begun noticeably to disappear (they had never been large), his sense of well being had greatly increased, and his occasional minor arthralgias and joint stiffnesses no longer occurred

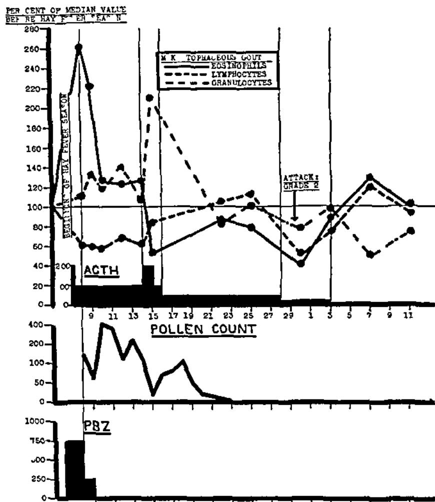


Fig 17 *The effect of chronic administration of ADACTAR (adsorbed adrenocorticotrophin Armour) on differential leukocyte patterns and upon hay fever in patient M K* (All blood counts were performed 24 hours after the last infection of Adactar 50 mg of this material in an average normal adult depresses the eosinophil count to below 20% of the basal value 8 hours following administration and gives a residual depression of eosinophil count to below 60% of the basal value 24 hours after injection)

prolonged course of ACTH was, of course, negative since his unresponsive adrenal would have masked any release of ACTH When the test was repeated within a few days after his long course of ACTH there again was no evidence of ACTH release

This patient appears to illustrate a previously undescribed endocrine syndrome An absence of adrenal cortical response to initial doses of ACTH with gradually improving response upon repetition of ACTH administration has been found by Forsham and his associates[10] to characterize an adrenal which is atrophic because of chronic understimulation by ACTH Such a response pattern is typically found in panhypopituitarism due to chromophobe adenoma In our patient this response pattern suggested chronic undersecretion of ACTH yet other observations showed normal secretion of most of the remaining pituitary hormones The tentative endocrine diagnosis indicated therefore appeared to be *hypopituitarism with respect to ACTH* Ideally one would wish to prove this diagnosis by demonstrating a decreased circulating level of ACTH However a recent report by Taylor Albert and Sprague indicates that current methods are not sufficiently sensitive to detect even normal circulating ACTH levels

Since we wished to observe the effect of ACTH both upon the patient s severe hay fever and upon his gout chronic administration of ACTH was deliberately withheld until well into the fall hay fever season He then was receiving 750 mg day of PBZ (tripelennamine) with only minimal symptomatic relief Before the hay fever season he had a median circulating eosinophil count of 251 and this increased to 678 during the first month of the hay fever season This eosinophilia presumably was not due to decreased 11 OS secretion since it was not accompanied by lymphocytosis

Daily administration of 100 mg /day of ADACTAR a long acting ACTH preparation was begun on September 9 The entire daily dose was given as a single injection throughout the study except on September 15 when an additional 100 mg was given a few hours later As expected from an individual with a chronically understimulated adrenal his hematological response (Fig 17) was subnormal for the first 24 hours but had become approximately normal by the end of 48 hours He required 250 mg of PBZ for relief of hay fever during the first 24 hours but has been symptom free and has used no PBZ since When ACTH was discontinued in October the hay fever season had ended His eosinophilia did not reappear at that time but instead, his eosinophil count reverted approximately to the level obtaining before the hay fever season

Fig 18 summarizes changes observed in purine metabolism and in

During his attack in the Autumn and Winter of 1948–49 his weight had fallen from 284 to 218 lbs, because of severe anorexia In spite of repeated attempts on our part to prevent a re gain of this weight he succeeded in the first 10 months of 1949 in reacquiring the entire 66 pounds Because we previously had observed the marked increase in appetite usually induced by ACTH the hormone's possible effects on his already huge intake caused concern After the first 8 days of ACTH however his new sense of well being appeared to give him the ability and willingness previously lacking to control his appetite This has persisted to the time of writing and he has gradually lost weight

By the end of the initial 8 day period M K s serum urate had fallen from 10 8 mg % to 6 95 mg % a value considerably lower than any previously observed and almost within our normal upper limit for adult men Simultaneously however his serum oxypurine level had risen to 3 75 mg % 12 times the average normal value The expected increases in urine urate/creatinine and in urate clearance/creatinine clearance were observed while oxypurine disappeared entirely from the urine Despite his marked decrease in serum urate concentration the observed changes in urate clearance/creatinine clearance in urine inorganic phosphate/creatinine and in urine potassium/creatinine were on the whole somewhat smaller than those ordinarily expected with the dosage of ACTH given It appeared likely that some persistent degree of adrenal unresponsiveness was present

A decrease in the daily dose of hormone to 50 mg /day on September 19 led promptly to a rise in serum urate and fall in serum oxypurine Urinary oxypurines once more reappeared The urate clearance/creatinine clearance ratio fell sharply and the oxypurine clearance/creatinine clearance ratio rose sharply

On September 29 the daily dose of ACTH was decreased to 25 mg /day An attack of acute gouty arthritis began the following evening and rapidly reached Grade 2 intensity Since the usual daily ration of 0 5 mg of intravenous colchicine had been continued during ACTH administration this attack was disturbing for we had come to rely upon the prophylactic potency of colchicine against such ACTH withdrawal attacks We had however overlooked the absence of diarrhoea since ACTH had been begun The patient s daily ration of colchicine was immediately increased to check the completeness of his colchicinization It very soon became apparent that at some point during ACTH administration a very marked increase in his tolerance for colchicine had occurred Fig 19 summarizes variations in M K s tolerance for colchicine during 1949 Prior to his long course of ACTH his tolerance for intravenous colchicine had averaged 0 42 ± 0 20 mg /day From October 1 to October 20 he tolerated a total of 24

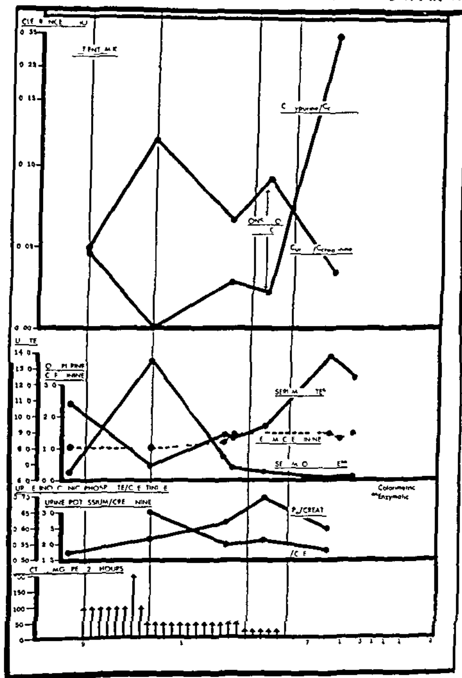


Fig 18 *The effect of chronic administration of ADACTAR (adsorbed adrenocorticotropin Armour) on urate metabolism on oxypurine metabolism and upon potassium and inorganic phosphate excretion in patient M K* (We are indebted to Dr Irving Wolin for referring this patient for study and treatment and for co operation and advice on orthopedic problems which arose during the patient s prolonged attack of gouty arthritis in 1948)

of the relatively unresponsive adrenals seen in other gout patients may also arise from mild degrees of chronic understimulation by ACTH Symptomatic relief afforded by ACTH in acute gouty arthritis apparently continues to be complete during chronic ACTH administration Our ability in 2 patients to confirm the reported diminution in size of tophi[9] may imply that were sufficient ACTH available much of the tissue pathology of gout might be reversible If confirmed in other patients the persistent increased tolerance for colchicine shown by this patient might prove valuable both in the treatment of gout and for certain other purposes

INABILITY OF ACTH EVEN TEMPORARILY TO RESTORE PURINE METABOLISM IN GOUT TO NORMAL

A review of the relationship between serum oxypurine levels and serum urate levels in gout patients has been undertaken to determine whether a spontaneous or ACTH induced decline in serum urate level is always associated with a marked rise in serum oxypurine level Fig 20 summarizes the minimum and maximum oxypurine levels and the corresponding simultaneously determined urate levels for a group of 9 gout patients Seven of the 9 had supernormal oxypurine levels at least on one occasion Maximum oxypurine levels occurred during chronic ACTH administration in 2 patients and following single doses of ACTH in 4 additional patients In the remaining instance a very high serum oxypurine level was noted shortly after recovery from acute gouty arthritis at a time when other metabolic criteria suggested a spontaneous increase in endogenous 11 OS secretion

Fig 8 records our observation that serum oxypurine levels tend to be low in untreated gout patients and are on the average somewhat lower during interval gout than during attacks In 7 of the 9 patients shown in Fig 20 serum oxypurine levels of 0 00 mg % were recorded at least once usually when urate levels were maximal

By projecting the lines connecting the minimal and maximal oxypurine values in Fig 20 to the left until the normal range for serum urate is entered it is apparent that in none of these 9 gout patients could a normal serum urate level have been attained without extremely high oxypurine levels being produced provided only that the linear relationship shown is a correct representation Actually the difficulty is even greater for in the few patients for whom there are sufficient observations to permit construction of a detailed curve relating serum urate and serum oxypurine the curve shows serum oxypurine levels to rise with accelerating rapidity as serum urate levels fall

The favorable effects of ACTH in gout shown by suppression of

mg of colchicine or an average of 1 20 mg /day approximately twice his maximum previous tolerance Beginning about October 25 he was gradually transferred to oral colchicine the transfer being completed by November 1 During the first week of November he tolerated an average of 0 75 mg /day of colchicine orally and was maintained completely on oral colchicine for the first time since July 1948 During the latter 2 weeks of November he took an average of 1 6 mg /day orally and continued symptom free

Twelve hours after the beginning of the attack of September 30 serum and urine studies uniformly suggested a higher 11 OS level than did those of September 27 The reason is probably to be found in

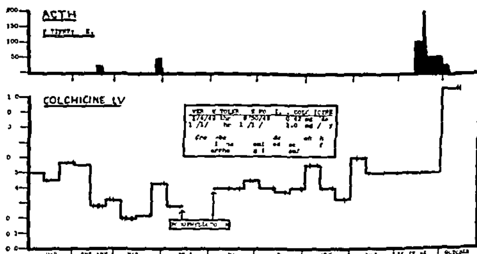


FIG 19 *Decrease in hypersensitivity to colchicine observed in patient M K during the chronic administration of Adactar*

the marked tendency of this particular attack to end spontaneously, for it was virtually over within 24 hours of its onset ACTH was completely withdrawn on October 4 There was no recurrence of the attack presumably because by this time the patient actually was fully colchicinized The serum urate concentration soon rose to above the pre treatment level while serum oxypurines disappeared The urate clearance was low and oxypurine clearance was high relative to creatinine clearance Marked lymphocytosis was present These changes persisted 8 days *after ACTH withdrawal indicating that rebound* still was defective

Therapeutic Implications

Study of this patient with almost ' pure tophaceous gout led to an apparently new endocrine syndrome hypopituitarism with respect to ACTH Finding this endocrine disturbance has suggested that some

standing chronic gouty arthritis free of articular symptoms to permit their tophi gradually to disappear and to bring their serum oxypurine levels from the low into the normal range In fact such doses of ACTH seem to return to gouty individual to a state resembling that which existed before he developed clinical gout that is they restore the state of asymptomatic inherited hyperuricemia

Fig 21 shows our hypothetical explanation for the inability of ACTH to restore purine metabolism in gout to normal The metabolic state produced in clinical gout by administration chronically of small

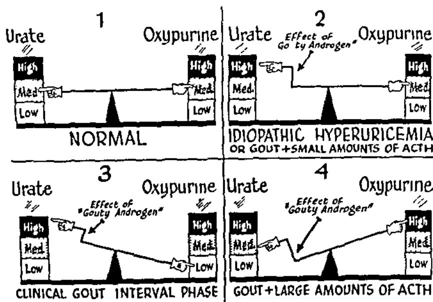


FIG 21 *An hypothesis to explain why normal serum urate levels and normal serum oxypurine levels cannot occur simultaneously in gout patients even when ACTH is given*

amounts of ACTH is shown as resembling that of asymptomatic hyperuricemia In 3 hyperuricemic relatives of gout patients studied to date serum oxypurine levels have been well within the normal range Administration of large amounts of ACTH produces a new unphysiological state The actual hypothesis suggests that the gouty androgen produces only an increase in serum urate without a proportionate decrease in serum oxypurine If correct purine metabolism in gout cannot be made normal by ACTH because 11 oxysteroids do not exactly oppose the effects of the abnormal androgen on purine metabolism since ACTH produces divergent changes on both urate and oxypurine levels

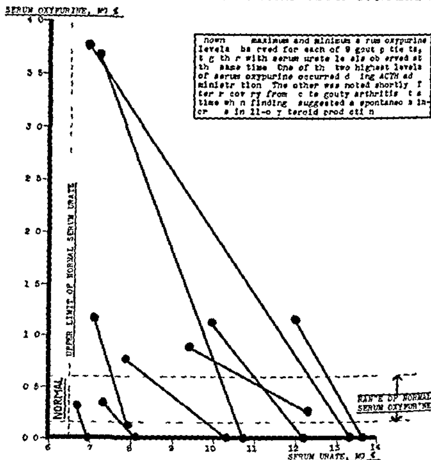


FIG 20 *Normal serum urate levels and normal serum oxypurine levels apparently can not occur simultaneously in gout patients even when ACTH is given*

acute and chronic articular symptoms and by softening of tophi naturally favored a first assumption that the simultaneously occurring decrease in serum urate represented a restoration of purine metabolism to normal Actually however this decrease in serum urate appears to accompany the production of a new disturbance in purine metabolism —normal serum urate with high serum oxypurine—which seems better tolerated than is gouty hyperuricemia

The spectacular effects of large chronic doses of ACTH in gout tend to mask the probable true value which chronic administration of relatively small doses of ACTH may have in this disease The gout patient is exceedingly fortunate in that his disease now has 2 potent remedies ACTH and colchicine both apparently acting at different loci Doses below 25 mg /day of ACTH apparently are sufficient when given with colchicine, to maintain patients even with long

which may be sufficiently severe to threaten life The physician must also recognize that his patient has lost some portion of the normal ability to meet that stress promptly

As yet, there is no specific treatment for such deficient ability to react promptly to 11 OS lack A rational approach is to reduce all chronic loads upon pituitary adrenal and cardiovascular function In gout the most common and obvious unnecessary load is that of obesity The physician may however also play a more active role When ever a stress may be anticipated or when it can be recognized while in progress the patient s defective mechanism for 11 OS mobilization may temporarily be assisted by administration of exogenous ACTH or 11 OS

The marked tendency of surgical operations and of acute myocardial infarction to precipitate attacks of acute gouty arthritis suggest these events constitute stresses to which the gouty commonly respond inadequately Acute myocardial infarction in fact most often terminates the course of gout Table 3 shows how a history of gout may lead to the uncovering of a grave and preventable surgical risk The patient whose data are given in Table 3 had the most unresponsive adrenals yet found in our gout group It was not until he had received 125 mg of ACTH (25 mg day) that a significant hematological response could be obtained from a final 50 mg dose of ACTH Through similar studies and through the prophylactic use of ACTH and 11 oxysteroids when indicated increasing understanding of the endocrine disturbances in gout should lead to increased safety for the gout patient For most gout patients this promises to be a truly important outcome of current endocrine studies and one which may equal in importance the improved treatment of the manifest symptoms of gout

SUMMARY

1 The inherited susceptibility to gout is believed to depend upon an abnormal adrenocortical androgen which controls the appearance of inherited hyperuricemia Androgens generally produce effects on urate metabolism opposite to those of ACTH or 11 oxysteroids The abnormal androgen is believed to produce androgenic effects on urate metabolism to a degree which is large compared to the masculinization it induces

2 Clinical gout appears associated with a second endocrine disturbance an impaired ability to respond promptly to 11 oxysteroid lack by increasing 11 oxysteroid production Instead the lack is permitted to persist and often to precipitate acute gouty arthritis Even when the attack does occur its stress seldom leads to early mobiliza

For therapeutic purposes, the inability of ACTH to restore purine metabolism to normal in gout is relatively unimportant ACTH can restore a state resembling asymptomatic inherited hyperuricemia and so far as we now know this state is quite as compatible with good health as is the possession of a normal serum urate level The finding is therefore chiefly important as a reminder that ACTH lack alone does not constitute gout

THE GOUT PATIENT AS AN INDIVIDUAL WITH A DEFECTIVE MECHANISM FOR IMMEDIATE NON SPECIFIC RESPONSE TO STRESS

The unfolding pattern of endocrine dysfunction in gout dictates an unconventionally sober view of the gouty man His gout attack appears to be an early warning of a serious glandular disturbance, for a history of clinical gout marks an individual as one with a deficient ability to meet relative 11 oxysteroid lack by promptly increasing 11 oxysteroid production Under minor stresses failure to increase 11 oxysteroid production may not become apparent The recent trend in endocrinology has been to emphasize the tendency of even slight stress to mobilize the pituitary-adrenal mechanism but it must also be recognized that this is often a biological luxury Ability to deal with lesser degrees of physical stress does not ordinarily require more than the basal amounts of 11 oxysteroid * Increased amounts of 11-oxy steroid become a necessity only when stress becomes more severe Unfortunately the regulatory disturbance in gout appears to involve the system necessary for mobilization of immediate defense against severe sudden somatic stress Certainly recent observations leave no doubt as to the wide variety of stresses injuries and diseases against which 11 OS may afford a critical degree of protection

This disturbance in the endocrine mechanism for mobilizing non specific resistance is the real danger to most gout patients Because of the age group in which gout ordinarily is seen and because the gouty appear more than ordinarily susceptible to hypertensive arteriosclerotic cardiovascular disease the physician who sees a gout patient should be aware of a very real possibility that his patient will within a limited number of years be forced to meet a stress usually vascular

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Ingle[30] has shown that adrenalectomized animals maintained on a constant daily dose of adrenal cortical extract may show quite normal resistance to stresses of moderate severity and may unlike untreated adrenalectomized animals show the usual increased nitrogen output of the alarm reaction Nevertheless even ACE treated animal do not show the ability to withstand maximal stress which is found in normals Apparently only when stress passes some critical degree of severity is extra 11 oxysteroid necessary for the animal's protection Clinically this is true as well A well maintained Addisonian can withstand minor stresses withou an increased requirement for adrenal cortical extract

therapeutic response to ACTH Presumptive evidence in one patient indicated the existence of "hypopituitarism with respect to ACTH In this patient unresponsiveness to initial doses of ACTH appeared referable to chronic understimulation of the adrenal cortex by the pituitary

5 In an interval gout patient administration of ACTH followed by withdrawal precipitates a state of 11 oxysteroid lack which frequently provokes acute gouty arthritis Administration of ACTH will terminate such a provoked attack or a spontaneous attack dramatically Unfortunately attacks so terminated tend to recur upon hormone withdrawal

6 Colchicine when given in full doses appears to exert marked prophylactic potency against ACTH withdrawal attacks of acute gouty arthritis This has made possible the development of a combined treatment of acute gouty arthritis in which ACTH is employed to terminate the attack rapidly and colchicine to prevent its return when ACTH is withdrawn Clinical trial of combined ACTH colchicine therapy in over 20 cases of acute gouty arthritis has shown this approach to provide the most rapid and effective management of acute episodes now available In almost all cases less than 100 mg of ACTH need be given

7 Although colchicine does appear to release small amounts of ACTH in man this action is slight evanescent and entirely inadequate to explain its therapeutic and prophylactic action in gout

8 The administration of ACTH alone cannot restore purine metabolism to normal even though serum urate levels may be lowered almost into the normal range by chronic administration of large doses As serum urate levels fall serum oxypurine levels rise to markedly supernormal values It appears to be impossible to obtain normal serum urate and serum oxypurine levels simultaneously in a gout patient through the use of ACTH

9 In one gout patient an hypersensitivity to colchicine became much less marked during chronic administration of ACTH and did not recur after hormone withdrawal In the same patient disappearance of hay fever and of its associated eosinophilia were observed within 48 hours after beginning chronic ACTH administration When ACTH was withdrawn the hay fever season had ended Following withdrawal the eosinophil count returned to the values obtaining before the hay fever season rather than to the high levels existing at the start of treatment

10 Chronic administration of ACTH has been studied in 3 patients Continuous freedom from articular symptoms softening and decrease in size of tophi and restoration of serum oxypurine concentrations to normal may be seen with doses of ACTH which generally

Table 3

A HISTORY OF GOUTY ARTHRITIS MAY INDICATE A POOR SURGICAL RISK ABSOLUTE UNRESPONSIVENESS TO 50 MG OF ACTH IN A PATIENT WITH ACUTE GOUTY ARTHRITIS PRECIPITATED BY A BLEEDING DUODENAL ULCER

(The attack began as it commonly does about 1 week after the bleeding episode and at the height of *hematopoietic regeneration as indicated by maximum reticulocytosis* The 25 mg test dose of ACTH produced only slight relief of symptoms and owing to a misunderstanding no further material was given The patient s response to repeated doses of ACTH is to be studied in the near future)

	10/4 49	10 14/49	10/21/49		
			50 MG ACTH		
			Before	After	Change
Eosinophils	——	250	269	303	+13%*
Lymphocytes	——	1116	1278	1653	+30%*
Granulocytes	——	4834	3778	6744	+78%†
Serum Urate	12 6	10 7	11 3	9 9	
Serum Oxypurine	——	1 10	0 29	0 00*	
Serum Creatinine	1 2	1 1	1 2	1 2	
Urine Urate/Creat	——	0 26	0 34	0 21	−38%
Urine Oxypurine/Creat	——	0 00	0 00	0 00	
Urine Phosphate/Creat	——	0 30	0 38	0 42	+12%
Urine Potassium/Creat	——	2 42	1 80	2 05	+18%
Urine Sodium/Creat	——	——	0 95	1 66	+75%*
Curate /Creatinine	——	027	036	026	−28%*

Starred items show changes suggesting that an actual decrease in 11 OS output may have occurred within the few hours after ACTH was given but none are beyond the possible *limits of spontaneous variation*

† Although ACTH produces an increased granulocyte count this finding is non specific and may not be taken to indicate an adrenal cortical response unless accompanied by significant eosinopenia or lymphopenia

tion of appreciable amounts of extra 11 oxysteroid A metabolic correlate of this disturbance is the defect of rebound seen when exogenous ACTH is withdrawn from gout patients

3 Failure of the gouty to respond to relative 11 oxysteroid lack is due to failure of the pituitary to release extra ACTH when presented with a normally adequate stimulus and not to unresponsiveness of the adrenal cortex to stimulation Preliminary observations suggest the ultimate locus of this disturbance to be in the hypothalamic control of pituitary ACTH release

4 An appreciable proportion of gout patients do show some quantitative diminution in the adrenal cortical response to exogenous ACTH, although this is ordinarily not sufficient to prevent a good

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do not exceed 25 mg day after the first few days These doses are not large enough to produce marked lowering of serum urate levels Chronic administration of fairly small doses of ACTH together with full doses of colchicine appears capable of returning a gout patient to a state of well being much like the state of asymptomatic hyperuricemia which ordinarily precedes the onset of clinical gout

11 The use of concurrent ACTH colchicine therapy to terminate acute gouty arthritis and a wider employment of the marked prophylactic potency of colchicine appear to be practical therapeutic measures immediately applicable to routine problems in gout The chronic administration of small daily doses of ACTH with or without colchicine remains an experimental approach which requires much additional study to assess its precise eventual role in therapy

ACKNOWLEDGMENT

It is a pleasure to thank Dr William D Robinson Director of the Rackham Arthritis Research Unit School of Medicine University of Michigan and Dr Leon Hellman of the Sloan Kettering Institute for Cancer Research for permission to discuss certain of their unpublished observations Generous supplies of pituitary adrenocorticotrophic hormone (ACTH Armour) were furnished by The Armour Laboratories through the cooperation of their Medical Director Dr John R Mote Dr Ernst Oppenheimer and Dr Fred E Houghton of the Research Division, Ciba Pharmaceutical Products have assisted our studies by making available a number of crystalline steroid hormones

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DISCUSSION

DR HUDSON HOAGLAND I would like to ask if such a gout patient as Mr M K is normally responsive to injection of adrenal cortical extract?

DR WILLIAM Q WOLFSON In the case of Mr M K who was virtually completely unresponsive to normal initial doses of ACTH, we do have some information on this point During his extremely severe polycyclic polyarticular attack last Winter we gave him a single 50 ml dose of Wilson aqueous adrenal cortical extract Subjective and objective improvement were apparent within 2 hours and by the following morning only minor residual symptoms remained Four hours after the adrenal cortical extract his eosinophil count had decreased 25% lymphocyte count was down 30% and urine urate/creatinine ratio had increased 24% Solely from these metabolic changes I do not think one can conclude anything definite about his sensitivity What is important is that a single dose of ACTH which we now know would have little effect on an ordinary patient with rheumatoid arthritis was able temporarily to terminate this severe gout attack which had been going on for months One must I suspect conclude that if anything he was normally sensitive or even hypersensitive to the steroids which were in the extract

The further outcome of this experience was distinctly instructive At that time we did not know that one must give colchicine to prevent the return of attacks relieved by corticoids He continued well for 36 hours and then explosively developed a most severe polyarticular attack of gouty arthritis Virtually every joint was involved in both arms and legs He stopped eating and probably because of the resulting shift to an endogenous high fat diet his serum urate rose to 18 1 mg % (colorimetric) of which over 90% was true urate by the uricase method His serum creatinine at this time was only 1 10 mg % This gave him a serum urate creatinine ratio of above 16 4 well over 3 times the average normal value and by far the highest value we ever have seen We frankly were alarmed by this urate level and decided to give him large amounts of 20% glucose intravenously as suggested by Dr Elmer Bartels The attack however was so severe that it was not until large amounts of narcotics had been given that it was possible to move his arms sufficiently to reach a vein adequate for the infusion

22

Modification of Blood Pressure by Cortisone and ACTH in Normotensives and Hypertensives

George A Perera

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This is not the time or place to review the relationship of the adrenal cortex to arterial hypertension except to say that the possibility of such a relationship was the reason for our interest in cortisone and ACTH

In studies conducted at the Presbyterian Hospital in New York we were able to demonstrate a decrease in the resting blood pressure in 3 of 4 uncomplicated hypertensive subjects following the continued administration of an adrenal cortical extract Furthermore, in other hypertensive patients the simultaneous use of this extract appeared to block the pressor effect of desoxycorticosterone acetate We were therefore anxious to determine whether cortisone might depress the arterial tension

Observations have now been made in 4 patients with hypertensive vascular disease one of whom was also a diabetic and one patient with Addison's disease (*Am J Med* 7 56 [July] 1949) All studies were undertaken after a suitable baseline all subjects were on an absolutely constant dietary and fluid intake and resting ' blood pressures were measured each morning by the same observer—the lowest readings of at least 7 determinations taken at ½ minute intervals with the subject lying quiet and relaxed in bed Cortisone was given intramuscularly in the acetate form usually in doses of 20 mgs every 6 hours for 8 days

Small changes in resting blood pressure were apparent in all patients These however were consistently greater than those observed in our clinic in control hypertensives treated with placebos or for similar periods of time In the hypertensive patients the arterial tension declined—generally after the period of treatment sometimes

during treatment This effect was not related to changes in plasma volume

In contrast, in the patient with adrenal cortical insufficiency maintained on constant amounts of salt and desoxycorticosterone the

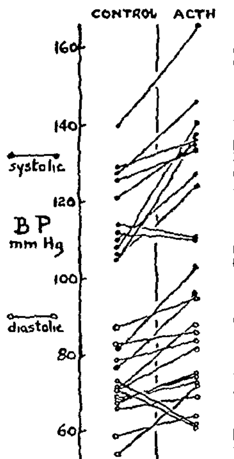


FIG 1 Effect of ACTH on B P

blood pressure rose more than would be expected on the basis of salt and water retention alone This has been seen in adrenalectomized animals by Guadino and recently by Knowlton and her group at our institution The difference in response of the Addisonian patient and the delayed effects on resting blood pressure in all patients imply that cortisone has no direct humoral action Furthermore the difference in the Addisonian and the hypertensives suggests that cortisone

requires the presence of intact adrenals for its depressor effect and may act as a pressor agent in the absence of the adrenals

We have observed the effects of ACTH on "resting" blood pressure in 13 patients These included a few of our hypertensives also patients

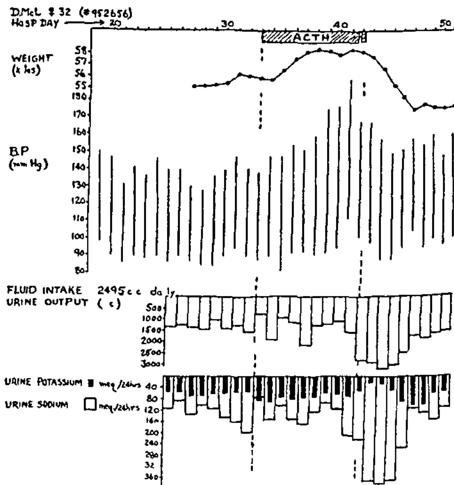


Fig 2 ACTH in hypertensive vascular disease

with rheumatoid arthritis and related disorders (being studied by Dr Charles Ragan) in whom we were permitted to make our own observations

A rise in blood pressure was noted in the great majority (Fig 1) The increase was not only a sequel to the disappearance of fever as many were afebrile The increase in blood pressure was not purely a function of dosage which varied from 15 to 50 mgs of ACTH every 6 hours The absence of consistent changes in pulse and the failure of the

blood pressure to drop after benzodioxane administration make it unlikely that the rise in tension is related to an increase in circulating epinephrine or norepinephrin Nor do we believe that the plasma volume is responsible Although direct determinations with T 1824 often indicated a rise secondary to hemodilution of 100 to as much as 800 cc in one subject the blood pressure could not be correlated with these changes and indeed rose sharply in a few individuals who failed to display significant fluid retention hemodilution or weight gain

Thus far we have insufficient data on cardiac output alterations and these have been confused further by the presence of fever in some patients prior to ACTH therapy Serial ballistocardiograms indicated an increase in cardiac output in one patient a decline in another—both of whom exhibited hypertension produced by ACTH It remains to be determined but it is within the realms of possibility that at least a part of the action of ACTH is due to the release of pressor steroids from the adrenal cortex

A final word of warning one patient with uncomplicated hypertensive vascular disease was given 100 mgs a day of ACTH for a period of 9 days (Fig 2) On the eighth and ninth day of treatment at the point of greatest blood pressure increase she developed a severe headache mental confusion anorexia and slight nausea There was minimal nuchal rigidity These cleared promptly when the drug was discontinued The dangers of hypertensive encephalopathy of changes secondary to excessive hypertension or fluid retention must be kept in mind

DISCUSSION

There was no discussion on this paper

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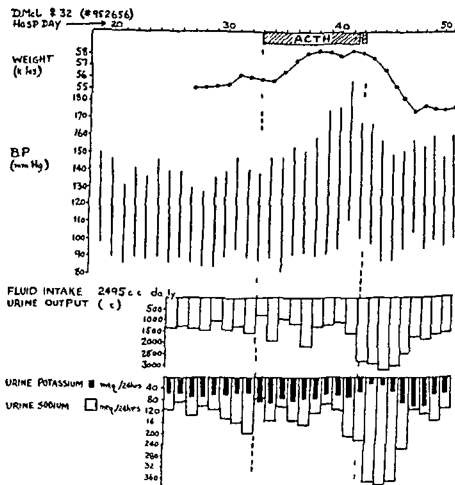


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only under anaerobic conditions. Under aerobic conditions they are actually inactivated by their tissues of origin.

Table I

FORMATION AND INACTIVATION OF VASOTROPIC PRINCIPLES BY NORMAL LIVER AND KIDNEY

	In Oxygen	In Nitrogen
1. *Hepatic Vaso-depressor (VDM)*		
VDM Formation	0	+
VDM Inactivation	+	0
2. *Renal Vaso-Excitor (VEM)*		
VEM Formation	0	+
VEM Inactivation	+	0

These vasoactive principles act on the metarterioles and precapillary sphincters of the terminal vascular bed. The renal factor VEM leads to a hyperreactive state of these muscular vessels as evidenced by their increased responsiveness to epinephrine and increased vasomotion favoring the constrictor at the expense of the dilator phase. The hepatic vasodepressor VDM has exactly opposite actions on these same vessels.

In the normal animal and man neither principle is present in the circulation in amounts detectable by our present methods of assay.[3] Following the induction of hypertension by either the application of Goldblatt clamps to the renal arteries or capping of the kidneys, a striking alteration occurs in the metabolism of both VEM and VDM.[4] The kidney exhibits a metabolic defect as a result of which VEM now appears in oxygen as well as in nitrogen. The ability to restrict VEM formation to the anaerobic state is lost. As a result, during the stage of acute hypertension VEM appears in the blood in increasing amounts. There is a parallel appearance of increasing amounts of hepatic VDM which attains concentrations equal to the VEM at the time when the blood pressure assumes the chronic hypertensive level. This release of VDM by the liver is due to a homeostatic response of this organ to the increased humoral content of VEM.

Several other specific alterations related to these hepatorenal mechanisms occur in the development of the renal hypertensive syndrome. During the acute stage the reactivity of the mesenteric vessels to the topical application of epinephrine becomes significantly enhanced, to return to normal during the chronic stage of the syndrome.[5] There is likewise an enhanced response of the mesenteric vessels to the intravenous administration of VEM. Finally, a very striking hyperplasia of the terminal vascular bed of the mesentery progressively develops.[6] This mesenteric hyperplasia is also seen in rats

23

Relation of the Adrenals to Alterations in the Renal VEM Mechanisms in Experimental Hypertension *

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NEW YORK CITY

The evaluation of the role of the adrenal cortex in hyper tension remains a problem of major importance It has recently gained additional urgency from the occasional development of hypertension in the course of therapy with ACTH or cortisone The relationship of this type of hypertension to essential hypertension in man is now a matter of active investigation in a number of laboratories These studies may be expected to provide valuable information which will bear directly on the problem of whether essential hypertension in man is due to a primary defect in adrenal cortical function or whether the adrenal cortex is merely an essential element in a chain of events re sponsible for hypertension

In view of the multiplicity of hypertensive states the soundness of this evaluation will be dependent upon the availability of specific criteria upon which such an assessment can be made

It is our purpose to describe experiments which have been con ducted in our laboratory over the past several years and which have revealed specific defects in a newly described hepatorenal circulatory homeostatic mechanism which are characteristic of experimental renal hypertension and essential hypertension in man These studies have established the existence of a hitherto unsuspected circulatory homeo static system[1] concerned with the regulation of the terminal vascular bed This system consists of an hepatic vasodepressor which we have termed VDM and identified as ferritin and a renal vasoexcitor VEM In the normal liver and kidney these principles appear *in vitro*

* The work described has been aided by Grants from The Josiah Macy Jr Foundation Eli Lilly & Company and the United States Public Health Service

Table 2

DETERIORATION OF VEM FORMING MECHANISM IN KIDNEYS OF ADRENALECTOMIZED RATS

(VEM quantitated on basis of duration of effect in rat meso appendix test + = 5 – 10 min ++ = 10 – 20 min +++ = >20 min)

Days After Adrenalectomy	*Number of Rats*	*VEM in Wash*	*VEM Formation in vitro in O_2*	*in N_2*	*Qo_2 wet weight cc/gm hr*
Controls	2	+	0	++	2.87
	2	+	0	+++	3.24
	2	+	0	+++	3.30
	2	++	0	+++	3.10
2 to 3	2	0	0	+	2.60
	2	0	0	0	2.79
	2	0	0	0	3.06
5 to 6	3	0	0	0	3.01
	3	0	0	+–	2.44
	3	0	0	0	2.40
8	3	+–	0	0	2.90

Controls represent kidneys removed from animal at time of adrenalectomy

Table 3

VEM FORMATION BY KIDNEY OF ADRENALECTOMIZED RATS RECEIVING DIFFERENT SUPPORTIVE THERAPY

(VEM quantitated on basis of duration of effect in rat meso appendix test + = 5 – 10 min ++ = 10 – 20 min +++ = >20 min)

	NaCl					*DCA*	*NaCl + DCA*	
Days After Adrenalectomy	6	10	1[illegible]	1	14	10		12
Wash	+–	0	+–	0	0	+	+	+
Oxygen	0	0	0	0	0	0	0	0
Nitrogen	0	0	+–	0	+–	++	+++	++
Qo_2	2.8	2.6	2.4	2.9	2.6	2.8	2.6	2.4

Our next concern was to investigate the possible bearing of these phenomena on the failure of adrenalectomized animals to sustain hypertension following constriction of the renal arteries or capping of the kidneys These studies were carried out on rats and confirmed

with spontaneous hypertension and hence may be considered a significant and specific index favorable to a similarity between essential and renal hypertension in the rat

Experiments in human essential hypertension have not been as complete as those in animals lacking the *in vitro* studies on the isolated kidney and liver but the findings in the peripheral blood as well as in

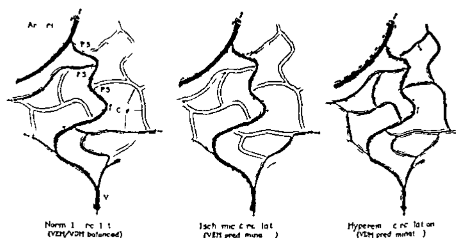


FIG 1 Diagrammatic representation of the alterations in the terminal vascular bed which are associated with the predominance of either VEM or VDM in the blood stream During VEM predominance the normally intermittent circulation through the endothelial capillaries is replaced by capillary ischemia resulting from the predominance of the constrictor phase of vasomotion at the precapillary sphincters The hyperemic circulation with an overall capillary flow during VDM predominance results from depression of vasomotion favoring the dilatation of the precapillary sphincters

renal vein and hepatic vein blood are identical in every respect to those we have just described for experimental renal hypertension

The relation of these changes in the hepatorenal mechanisms to the function of the adrenal cortex has been investigated in dogs rabbits and rats the most extensive studies being on the rat and particular emphasis being given to the renal VEM system [8] These studies have revealed the dependence of the renal VEM mechanisms on the adrenal cortex and its hormones Following adrenalectomy there is a *rapid deterioration of the renal VEM system* as a result of which the kidney can no longer form this principle This defect persists in adrenalectomized rats supported by salt alone Supportive therapy with DCA or DCA and salt or with adrenal cortical extract and salt preserves the renal VEM mechanism The adrenalectomized animal also exhibits a progressive loss of the responsiveness of the terminal vascular bed to the intravenous administration of VEM

in vitro on either anaerobic or aerobic incubation producing instead in many instances a vasodepressor principle The capped kidneys of the hypertensive animals with intact adrenals regularly exhibited both aerobic and anaerobic VEM formation

Table 4

DETERIORATION OF VEM FORMING MECHANISM IN CAPPED KIDNEYS OF ADRENALECTOMIZED RATS

(VEM quantitated on basis of epinephrine response in rat meso-appendix test + = 0 – 15 min ++ = 15 – 25 min +++ = >25 min)

RAT NO	VEM IN WASH	VEM FORMATION *in vitro* in O_2	VEM FORMATION *in vitro* in N_2	RAT NO	VEM IN WASH	VEM FORMATION *in vitro* in O_2	VEM FORMATION *in vitro* in N_2
Intact Adrenals Capped Kidneys				*Bilateral Adrenalectomy Capped Kidneys*			
68	++	++	+++	3 9	0	0	VD 21 min
90 74	+++	+++	+++	62 63	0	0	traces VD
28 76	traces VE	++	++	65	0	0	VD 15 min
84	++	++	++	66 94	0	VD 17 min	VD 16
154	+	+++	++	90	0	VD 21	VD 26
162	+++	+++	+++	91	0	VD 24	VD 18
3 B	++	+++	++	114	traces VD	0	VD 15
				133	traces VD	traces VD	VD 12
				110	0	0	0

The animals with intact adrenals exhibited the previously described hypersensitivity to epinephrine This was absent in the adrenalectomized group The enhanced reactivity to the intravenous injection of VEM of the mesenteric arterioles observed in the hyper tensive animal was absent in those in which the adrenals had been removed Finally the mesenteric hyperplasia so regularly seen in the renal hypertensive rat was absent or minimal in the adrenalectomized group and those changes which did occur arose during the brief hypertensive period between the removal of the first and second adrenal and did not progress thereafter

It would seem permissible to infer from these observations that a very specific set of metabolic and vascular phenomena relating to the renal VEM mechanism both in the normal and hypertensive state is dependent upon the integrity of the adrenal cortex These findings however cannot be used as a basis for resolving the question as to whether the adrenal plays a primary role in hypertension Neverthe less their occurrence in animals and man in both experimental renal and spontaneous hypertension suggests that they may be used as

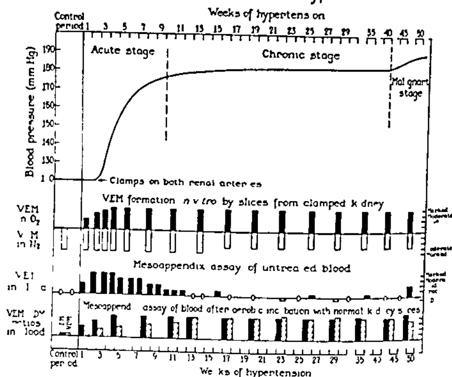


FIG 2 Semidiagrammatic representation of the alterations in the VEM and VDM mechanisms in experimental renal hypertension in the dog Note the onset of VEM formation by the clamped kidney in oxygen which leads to the appearance of VEM predominance in blood during the acute stage of hypertension The neutral blood assays which are usual during the chronic stage of hypertension are due to the parallel appearance of hepatic VDM in amounts which neutralize the effect of VEM in the rat mesoappendix test The presence of VDM in bloods containing both VEM and VDM is demonstrated by inactivating VEM by aerobic incubation with normal kidney slices a procedure which unmasks the VDM present

previous observations that hypertension does not occur under these conditions after bilateral adrenalectomy [9] The blood pressure course of parallel series of normal and adrenalectomized animals with bilateral kidney caps was followed for about 3 months and demonstrated the inability of the adrenalectomized salt supported rat to develop hypertension The several criteria which we have described above to be regularly present in the hypertensive animal with intact adrenals were then examined The adrenalectomized capped animals showed no VEM in the circulation Their kidneys failed to produce VEM

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162	+++	+++	+++	91	0	VD 24	VD 18
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criteria to evaluate the nature of the hypertension induced by ACTH cortisone desoxycorticosterone and other adrenal hormones

Preliminary experiments (unpublished data) utilizing these criteria have been carried out on rats made hypertensive with desoxycorticosterone acetate following the studies of Selye and his associ-

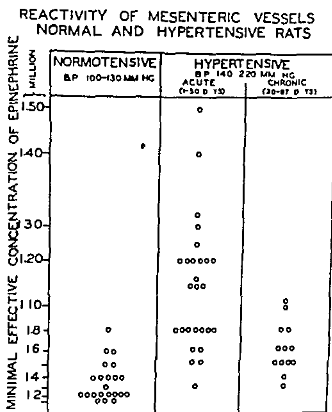


FIG 3 Alterations during the evolution of the hypertensive syndrome in rats of the reactivity of the terminal mesenteric vessels to the topical application of epinephrine

ates[10] Elevations in blood pressure were achieved from the average normal in our rats of 100–110 mm Hg to hypertensive levels usually between 150–200 mm and most frequently between 170–180 mm The duration of treatment with 5 to 10 mg of DCA daily ranged from 45 to 63 days In a number of animals a unilateral nephrectomy was carried out to exaggerate the hypertension The DCA induced hypertension was unassociated with any alterations in the vasotropic mechanisms such as those we had regularly observed in renal hypertension or essential hypertension in man There was no VEM formation by

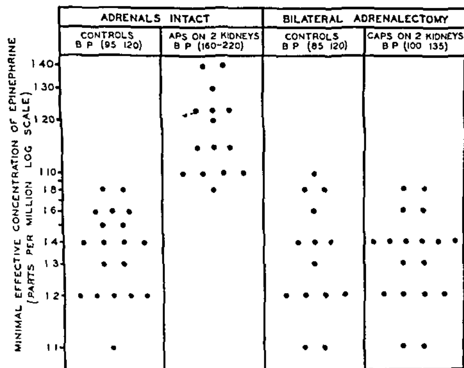


Fig 4 Comparison of the reactivity of the mesenteric terminal vascular bed of rats to the topical application of epinephrine in animals with kidney caps as modified by bilateral adrenalectomy

the kidneys of these animals in oxygen No VEM could be detected in the blood There was no increased responsiveness of the mesenteric vessels to epinephrine or to the intravenous injection of VEM and no hyperplasia of the mesenteric capillary bed The absence of these phenomena would suggest that the DCA hypertension in rats differs basically from experimental renal hypertension and essential hypertension in man In our strain of animals no periarteritis nodosa was observed These experiments are being extended with the utilization of DCA in pellet form as most recently recommended by Selye

We are now engaged in similar studies on the effects of ACTH and cortisone in both animals and man utilizing these various criteria to evaluate the relation of the hypertensive states caused by these hormones to experimental renal hypertension and essential hypertension in man

criteria to evaluate the nature of the hypertension induced by ACTH cortisone desoxycorticosterone and other adrenal hormones

Preliminary experiments (unpublished data) utilizing these criteria have been carried out on rats made hypertensive with desoxycorticosterone acetate following the studies of Selye and his associ

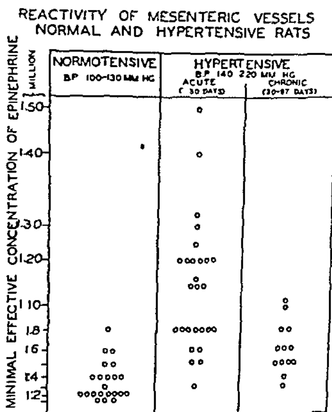


Fig 3 Alterations during the evolution of the hypertensive syndrome in rats of the reactivity of the terminal mesenteric vessels to the topical application of epinephrine

ates [10] Elevations in blood pressure were achieved from the average normal in our rats of 100-110 mm Hg to hypertensive levels usually between 150-200 mm and most frequently between 170-180 mm The duration of treatment with 5 to 10 mg of DCA daily ranged from 45 to 63 days In a number of animals a unilateral nephrectomy was carried out to exaggerate the hypertension The DCA induced hypertension was unassociated with any alterations in the vasotropic mechanisms such as those we had regularly observed in renal hypertension or essential hypertension in man There was no VEM formation by

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Studies on the Influence of Adrenocorticotrophin in Acute Nephritis, in Simple Nephrosis and in Nephrosis with Azotemia

Edith B Farnsworth

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL CHICAGO

PART I ACUTE NEPHRITIS

Two cases of acute nephritis were observed during treatment with ACTH (Armour) The first patient R L was a 12 year old girl in whom a severe acute nephritis had persisted unabated for 6 weeks Fig 1 gives the system of administration the blood urea and cholesterol both of which decreased during administration escaped after discontinuation and again decreased when the medication was restarted The urine color changed from dark red to straw colored on the sixth hospital day The blood pressure (Fig 2) rose in the first few days of treatment and one reading of 220/136 was recorded The urine protein also rose at first After this response however the blood pressure came down under treatment and tended to rise when treatment was suspended Persisting signs and symptoms at time of discharge were (1) a diminished but still present albuminuria (2) moderate elevation of blood cholesterol and (3) slight elevation of diastolic blood pressure The attempt was made to carry the patient with one injection daily of 25 mgms of ACTH under which system the discharge condition has been fairly well maintained the patient is gaining weight and is attending school

The second case C H is that of a 5 year old girl presenting a rather classic acute nephritis of several weeks duration In this patient also the smoky urine turned straw colored on the sixth day of treatment the blood urea came down to normal limits (Fig 3) escaped during discontinuation of treatment and decreased again on the second course

In both of these patients notwithstanding ACTH in sufficient quantity to suppress the eosinophil count edema did not appear and changes in body weight were inconspicuous

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DISCUSSION

DR R A CLEGHORN I want to say just one word I have had the opportunity of investigating adrenalectomized animals maintained by small amounts of hormone and they show a hypo responsivity to a variety of drugs including epinephrine barium chloride and pitressin These animals were not in adrenal insufficiency

DR J S L BROWNE I would like to ask Dr Shorr how long he maintained the hypertension with DCA?

DR EPHRAIM SHORR DCA was given in doses of 5 to 10 mg for from 43 to 63 days Hypertensive blood pressures were usually noted approximately 2 weeks after the injections were begun

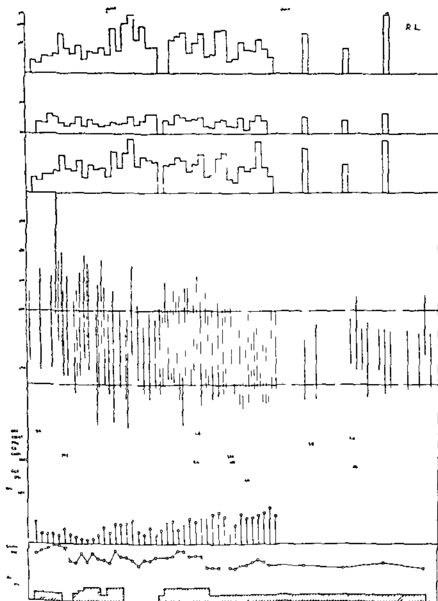


FIG 2 R L Electrolytes (Na K Cl) blood chem weight

PART II NEPHROSIS WITH CHRONIC NEPHRITIS

The first case in the chronic series is that of a 26 year old male in whom marked albuminuria was discovered in 1945 In October of 1948 he was hospitalized with severe hypertension uremia massive

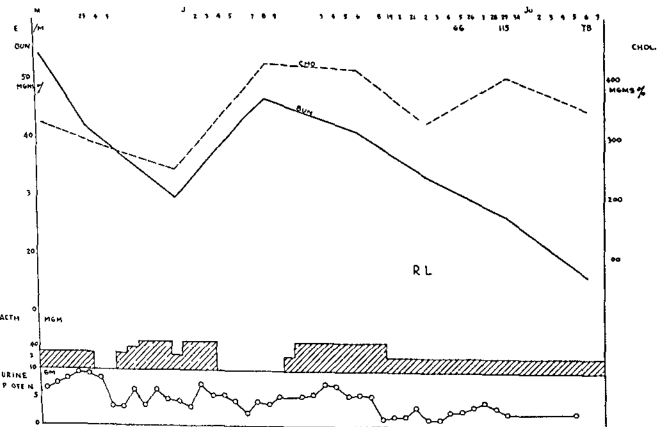


Fig 1 R L BUN chol eosin urine protein

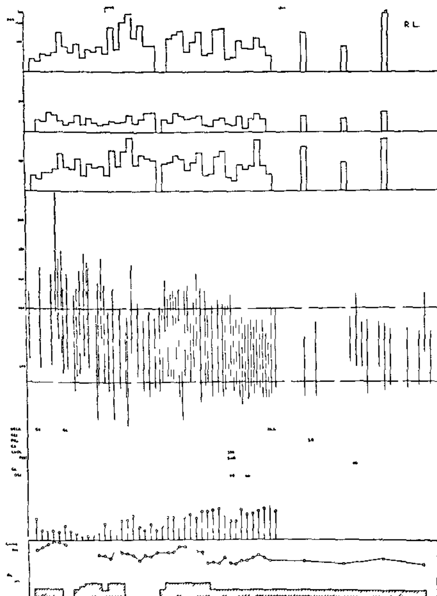


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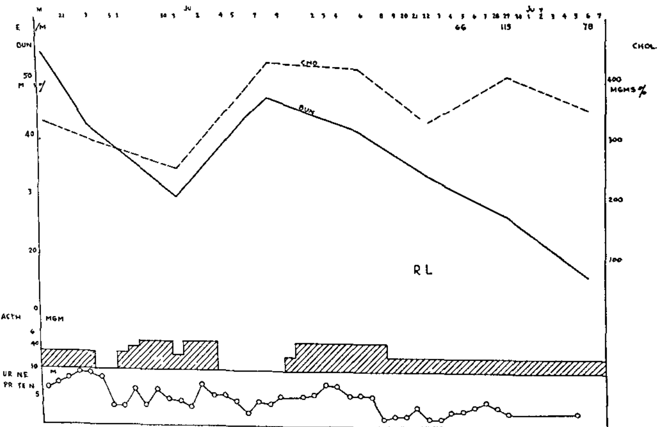


Fig 1 R L BUN chol eosin urine protein

edema convulsions and papilledema Determinations of renal filtration rate by Mannitol resulted in an average of 8 cc/min, and by endogenous creatinine 15 cc/min He received ACTH (Armour) 25 mgms twice weekly from March 11 until June 19 when he was hospitalized for intensive treatment and studies Fig 4 shows the blood urea and cholesterol throughout the course Fig 5 shows the body weight and the blood pressure The weight increased somewhat during administration diuresis began several days after discontinuation and became profound at which point the blood pressure lowered and stabilized positive nitrogen balance became established (Fig 6) and the plasma proteins rose to normal The carbon dioxide combining power also rose as did the serum calcium (Fig 7) and the inorganic phosphate declined from a peak of 13 4 mgms on March 25 to 3 8 on August 4 The patient was given a NaCl intake of 300 mgms and the 24 hour output in milliequivalents of Na K Cl and P are represented on the same graph Here also the follow up management has been a problem, and periods of daily 25 mgm injections have been employed as well as an interval system of 100 mgms in divided doses covering one day every week In this case also the condition on discharge has been fairly well maintained

The second case was a man of approximately the same age group who had come under our observation a year ago as an example of uncomplicated nephrosis, with perfect renal function and normal blood pressure During the year from May of 1948 until May of 1949 his renal filtration rate was found to decrease by around 50% and the diastolic blood pressure to rise moderately Moderate azotemia developed He was hospitalized on July 17 placed on 700 mgm salt intake and treated with ACTH according to the indications on Fig 8 On each course of treatment the excretion of sodium and chloride was promptly suppressed the urine volume decreased and the body weight rose The excretion of potassium (Fig 8) tended to increase slightly The effect upon phosphate was negligible After discontinuation of the medication diuresis occurred accompanied by a sharp drop in body weight and a rise in eosinophils After the third course the patient lost approximately 30 lbs in 5 days The output of sodium tended to exceed that of chloride during the diuretic interval The nitrogen balance (Fig 9) which became markedly negative after two days on ACTH shifted to the positive several days after withdrawal The addition of Perandren 25 mgms daily during the third course of ACTH appeared to shove the balance in the positive direction During the 30 days which followed the massive diuresis the urinary protein diminished to 0 5–1 5 grams daily while the blood proteins built up to nearly normal levels Contrary to the foregoing history the blood

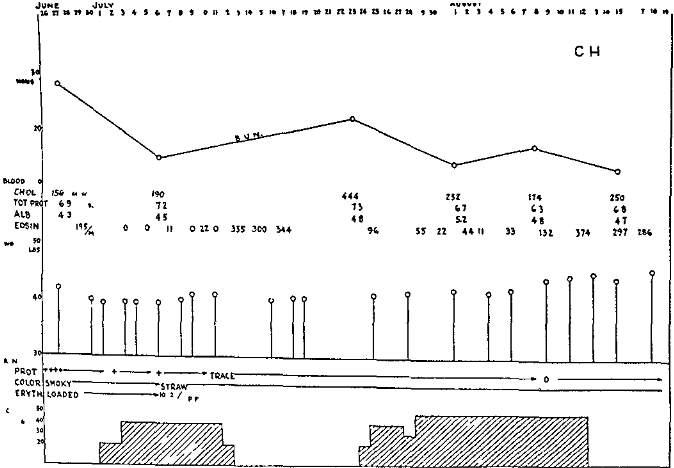


Fig 3 C H BUN chol tot protein alb eosin weight urine protein color

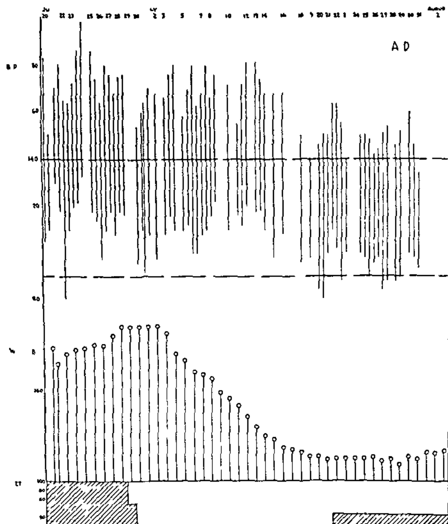


Fig 5 A D B P and weight during inten ive therapy

pressure tended to rise during this period and the pulse rate to ac celerate (Fig 10) The basal rate was found to be −4

PART III

The next 3 cases are classified as the nephrotic syndrome un complicated The first (M D) is a 3 year old girl whose treatment weight curve urinary protein and blood cholesterol and proteins are presented on Fig 11 along with the eosinophil counts Note that

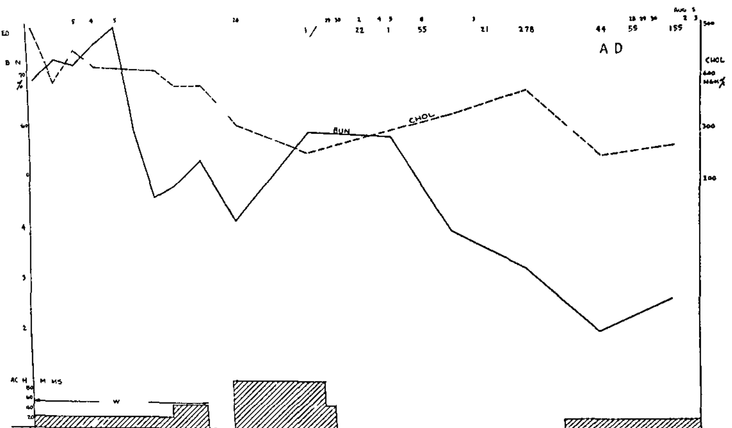


Fig 4 A D Eosin BUN chol from beginning of treatment

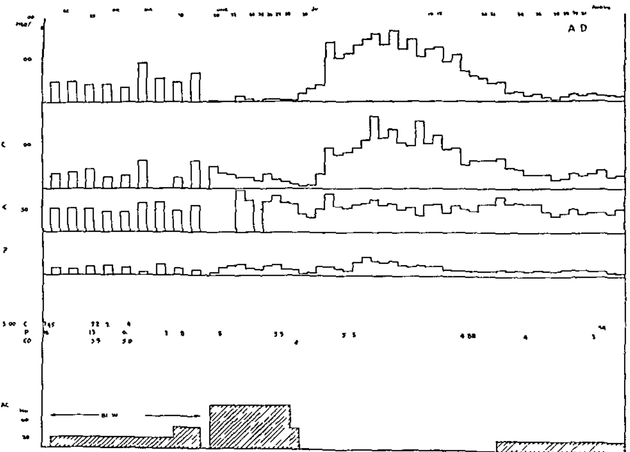


Fig 7 A D Electrolyte (Na Cl K P) output, blood Ca P CO

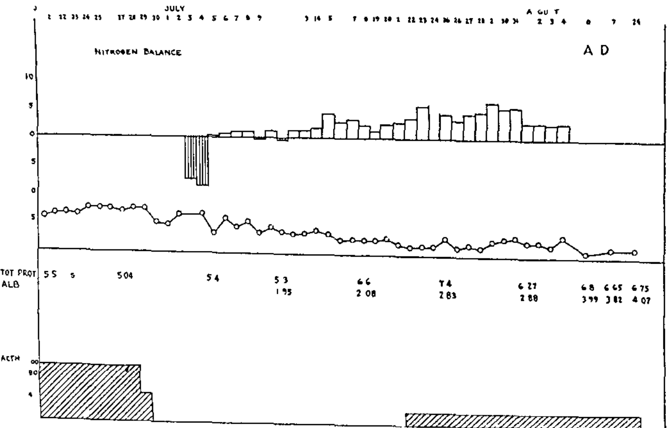


FIG 6 A D N balance urine protein blood proteins

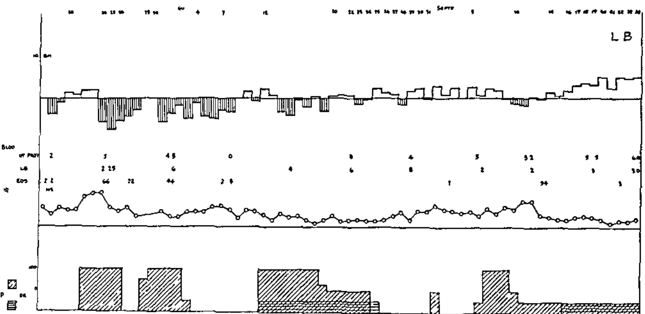


Fig 9 L B N balance blood proteins eosin urine proteins

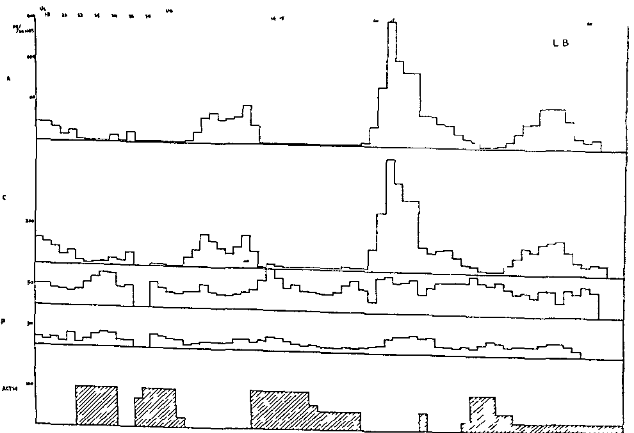


FIG 8 I B Electrolyte (Na Cl K P) output

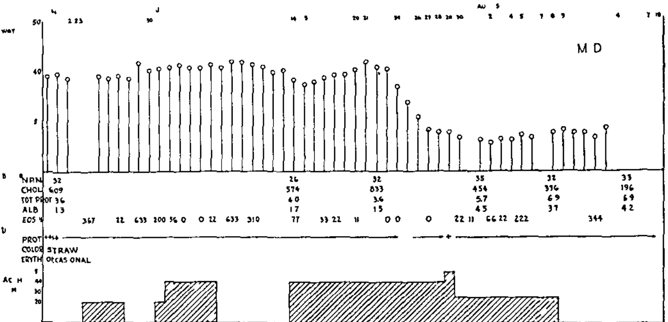


Fig 11 M D Weight blood chem urine protein

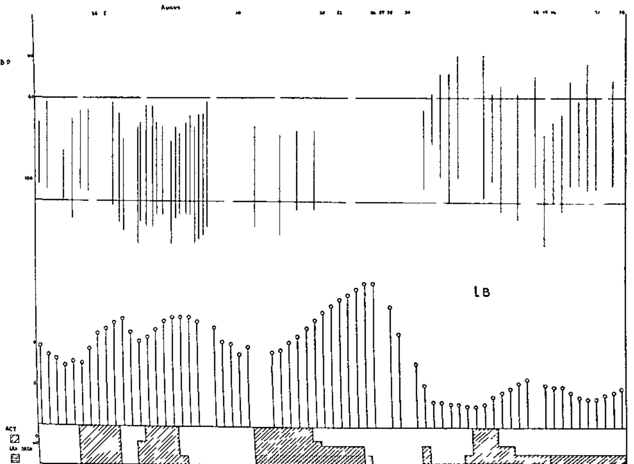


Fig 10 L B BP weight

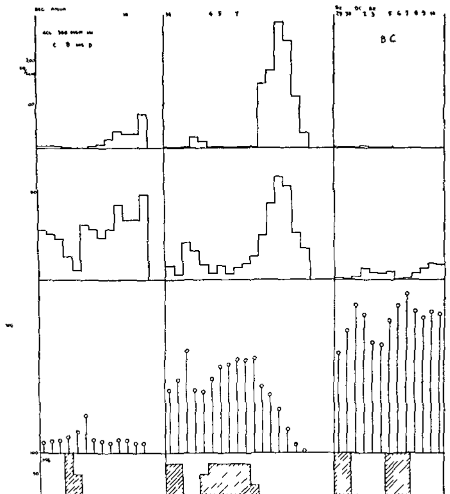


FIG 12 B C Na and Cl excretion and weight curves during several types of diuresis

The blood urea came down to normal limits and the blood proteins approached normal concentration Both of these patients underwent a massive diuresis of water and salt after withdrawal of ACTH in which the sodium excretion tended to exceed the chloride

Results in the uncomplicated nephrotic syndrome were more variable One patient underwent diuresis during the third course of ACTH and the blood chemistry reverted to normal within 2 weeks The second patient demonstrated 2 types of diuresis the one presumably referable to pituitrin the other to ACTH Improvement in blood cholesterol and proteins and urinary protein loss followed treat

diuresis failed to occur during or after 2 courses of ACTH although the eosinophil count was significantly reduced After a profound diuresis which took place during the third course of therapy the blood cholesterol came down rapidly to normal and the blood proteins rose The only residual manifestation of her disease which remained at the time of discharge from the hospital was a trace of protein in the urine

The second case a 23 year old girl who presented a typical picture of nephrosis with amenorrhea illustrates several diuretic situations (Fig 12) In January after 2 days treatment she had a copious almost salt free diuresis followed by a second phase of increasing salt excretion In May after a longer course of therapy she threw off a large amount of sodium chloride after withdrawal In September the slight diuresis which occurred was only the posterior pituitary type and was unaccompanied by sodium diuresis Fig 13 shows her hospital course in May during which she lost approximately 24 pounds the blood cholesterol and urine protein declined and the plasma proteins mounted On July 26 all follow up therapy was discontinued By August 17 the cholesterol had risen to 740 mgms edema had reappeared and the incidence of an upper respiratory infection resulted in complete relapse

The third case (J McL) was a 36 year old male with anasarca, ascites albuminuria hypoproteinemia and hypercholesterolemia of long standing His electrolyte output weight curve nitrogen balance and eosinophil counts are given in Fig 14 This patient was noteworthy for certain eunuchoid characteristics of skin and hair and for his refractoriness to ACTH as it was employed Four courses were given with the usual response reflected in eosinophil count and nitrogen balance A meager increase in sodium chloride and water excretion followed the third course with a loss of around 12 pounds in body weight but the diuresis was quite inadequate

SUMMARY

The inflammatory signs associated with acute nephritis subsided the azotemia disappeared and proteinuria diminished or disappeared Blood pressure declined under ACTH and escaped during withdrawal

In one case of advanced chronic nephritis the blood pressure was consistently reduced after ACTH diuresis and has remained at the lower level from mid July until the present At the last reading it was 138/84 The blood urea shifted from 69 to 21 mgms phosphate from 10 5 to 4 9, calcium from 7 3 to 9 6 albumin from 1 3 to 4 6

In a less advanced case of chronic nephritis the blood pressure rose after ACTH diuresis and has tended to remain at the higher level

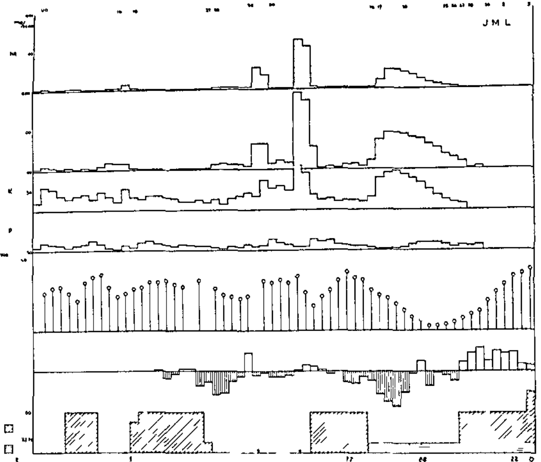


Fig 14 J McI Electrolytes weight curve N balance eosin

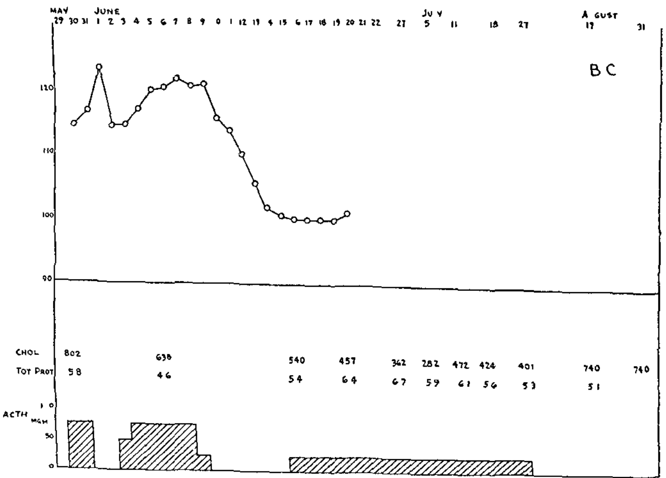


FIG 13 B C Weight curve with improvement in bl od ch l and pr teins an l r l

we have regularly observed an inability of the kidney to form the renal vasoexcitor VEM This property is restored by treatment with desoxycorticosterone acetate We have also shown by experiments in adrenalectomized animals that the integrity of the renal VEM mechanism is dependent upon adrenal cortical activity as I have just pointed out in my presentation before this group

The possibility therefore exists that the action of ACTH in causing diuresis in the clinical conditions just described by Dr Farnsworth may result from a stimulation of adrenal cortical activity and the consequent repair of an ineffective renal VEM mechanism The mechanism might then release VEM into the blood stream to counteract the antidiuretic effects of VDM This inference is now under investigation

DR ROGER A LEWIS In view of the improvement when the ACTH was discontinued I wonder if anybody has had any experience with cortisone and would venture an opinion as to whether cortisone would show an effect on withdrawal rather than when it was being given?

DR WALTER BAUER Has anyone here had any experience with cortisone in treatment of these adrenal diseases?

DR GEORGE W THORN There was a marked sodium diuresis lasting 3 days and a depressed 17 ketosteroid excretion suggesting a transitory inhibition of the patient s adrenal cortex

DR S SPECTOR (University Hospitals of Cleveland and Western Reserve University Medical School) We have been interested in the use of ACTH in children with nephrosis showing very minimal signs of nephritis To date we have treated 1 patient a 5 year old white child who had his nephrosis for a period of 2½ years During that period his albuminuria was constant and he had varying degrees of edema and ascites In the 8 months preceding therapy with ACTH the edema and ascites were marked and the child required an abdominal paracentesis frequently

During the control period his eosinophil count ranged between 600 and 1 000 cells per cubic millimeter He excreted approximately 2½ grams of albumin daily His total blood protein was 3 grams % of which 1 2 was albumin Blood cholesterol measured 600 milligrams %

With the institution of Armour ACTH at a dosage of 10 milligrams q 6 h the first change was a marked fall in the eosinophil count to approximately 60 cells per cubic millimeter This eosinopenia persisted throughout the 10 day period of therapy The uric acid

ment with ACTH and relapse occurred several weeks after withdrawal of medication Regular menses had been reestablished and were again suspended A third patient proved almost refractory to treatment by ACTH although the usual drop in eosinophil count was obtained

In no instance did the eosinophil count fail to drop to zero or approximately zero even though electrolyte and other responses were variable

Potassium diuresis was slight or absent in all cases

Glycosuria was observed at times in 2 children Serum glucose was frequently determined on all adults under intensive study Only 3 occasions were noted in which the blood sugar exceeded 100 mgms %

The blood cholesterol was substantially reduced in all examples of each syndrome and it tended to rise when therapy was discontinued

DISCUSSION

DR WILLIAM WALLACE (House of the Good Samaritan Boston) We have treated so far 2 patients with subacute nephritis with the nephrotic picture Both children have shown marked eosinophil response One child showed no diuresis at all The second child diuresed the day following the second course of 5 day ACTH administration The electrolyte pattern of the diuresis was that as though an ultrafiltrate was being lost We could find no evidence of excess chloride appearing

DR EPHRAIM SHORR I am tempted to speculate about the possible relation of these phenomena to the renal and hepatic principles VEM and VDM with which our laboratory has been concerned The hepatic principle VDM which we have identified as ferritin has been found in our laboratory (Baez Mazur and Shorr *Federation Proc*, 7 5 1948 and 8 7, 1949) to exert a profound antidiuretic effect in animals We have also observed that VDM is regularly present in considerable amounts in all states of oliguria which we have so far studied These include decompensated hepatic cirrhosis, simple nephrosis nephrosis with chronic nephritis and congestive heart failure with edema This principle is present not only in blood but in edema fluid as well In hypertension in both animals and man VDM is present in blood but along with it are physiologically equivalent amounts of the renal vasoexcitor, VEM Hypertensive patients with both VEM and VDM present in the blood exhibit no antidiuretic phenomena hence we infer that the antidiuretic effects of VDM are counteracted by the concurrent presence of VEM

In chronic nutritional cirrhosis in rats, due to low protein diets

weighing 58 lbs The accumulation of edema continued so that 3 weeks following her discharge from the hospital she weighed 84 lbs

S S—a 3½ year old girl with the nephrotic syndrome of 10 months duration She was admitted to the hospital weighing 45 lbs At the onset of her illness 10 months before she had weighed approximately 30 lbs She was extremely edematous had proteinuria with no evidences of glomerular damage or loss of renal function The serum proteins were low and the cholesterol elevated Her blood pressure and heart were normal ACTH (Armour) was administered for 13 days in the following amounts

1st to 9th days	50 mg daily
10th day	25 mg
11th day	50 mg
12th day	65 mg
13th day	80 mg

The ACTH was discontinued because of tachycardia Diuresis began on the tenth day of ACTH therapy and continued after it was discontinued In a 10-day period (from the onset of diuresis) there was complete loss of edema the weight falling from 47 lbs to 29 lbs The child was discharged from the hospital 2 days later weighing 30 lbs At home for a 10 day period her edema reaccumulated to a body weight of 38 lbs ACTH (Armour) was again given for 19 days (80 mg daily) There were no apparent signs of toxicity After the fifth day of ACTH therapy diuresis began and continued for 12 days her weight declining from 40¾ lbs to 29 lbs On small single daily doses of ACTH (10 to 12 5 mg daily) there has been a slow increase in weight Of great interest were the increase in serum proteins and return of the blood cholesterol to normal values Proteinuria continued

Summarizing the significant findings in these two nephrotic patients

1 ACTH (Armour) induces diuresis with loss of edema This effect is temporary and disappears some days after the withdrawal of ACTH

2 Elevated NPN declines to normal levels

3 Elevated blood cholesterol is depressed to normal levels

4 The serum protein concentration increases

DR EDITH B FARNSWORTH By way of conclusion of course I don t believe it is necessary to explain that we are not offering these as examples of cures We are attacking in this field a very complicated metabolic problem and with very primitive criteria to guide our attack

However I do believe that these data justify us in considering a more fundamental etiology to the disease than we had hitherto thought

creatinine ratio which was high initially increased only slightly The first urinary change which was noted was an initial increase in the albuminuria The next change occurred on the sixth day of treatment and was that of a fall in the albuminuria to 1 72 grams per 24 hours On the sixth day urinary output rose as did the sodium and chloride output Both reached a peak on the eighth day At that time potassium output was increased although the concentration remained unchanged Between the sixth and tenth day of therapy, the child lost 4 kilos almost 25% of his body weight, and his urine became albumin free Following the completion of therapy there was a rapid rise in blood albumin over the next 4 days to a level of 3 4 grams % and a marked fall in cholesterol to 180 milligrams % His eosinopenia although less marked persisted

The child has now been followed for almost 6 weeks since treatment has been stopped and despite one respiratory infection he has remained free of edema and free of albuminuria

DR MILTON RAPOPORT (The Children s Hospital of Philadelphia) We have administered ACTH (Armour) to 2 children with the nephrotic syndrome at The Children s Hospital of Philadelphia and feel that our observations incomplete as they are may be of interest

C M —a 7 year old girl with the nephrotic syndrome of 4 years duration On admission to the hospital 8/5/49, she was grotesquely edematous weighing 95½ lbs Two months before she had weighed 58 lbs She had hypertension (BP 140/108) poor renal function, azotemia hypoproteinemia hypercholesterolemia and proteinuria ACTH was given for 12 days as follows

1st day	20 mg
2nd 3rd 4th days	30 mg
5th day	50 mg
6th 7th 8th 9th 10th days	60 mg
11th and 12th days	80 mg

and was discontinued because she developed signs of cardiac failure (extra systoles cardiac dilatation and tachycardia)

On the eighth day of ACTH (Armour) administration there was an appreciable increase in urinary output so that her weight gradually decreased to 91 lbs on the day ACTH was discontinued Tremendous diuresis continued, so that 10 days after ACTH therapy was stopped her edema had entirely disappeared and her weight had fallen to 54 lbs (a loss of 41 lbs) Other findings of note were a decline in serum nonprotein nitrogen (NPN) from 47 mg /100 cc to 24 mg /100 cc and in serum cholesterol from 992 mg /100 cc to 464 mg /100 cc Serum proteins were unchanged and the proteinuria continued at the same level Her blood pressure was unchanged Four days after at ... of 54 lbs she was discharged from the hospital

In the 6 patients with lymphomatous tumors there was a dramatic and progressive decrease in the size of enlarged lymph nodes and of enlarged spleens during administration of ACTH or cortisone acetate Definite involution of lymphoid masses was first apparent after 3 days of administering ACTH and after 6 days of giving cortisone acetate In the 2 patients with carcinoma there was no obvious change in the clinical course of the disease during or after giving ACTH

Of the 6 lymphomatous patients studied 2 patients (lymphosarcoma [Fig 1] and lymphatic leukemia [Figs 2 and 3]) have shown

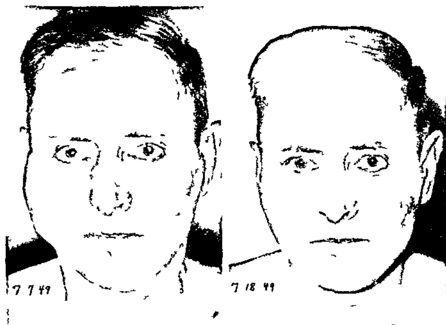


Fig 1 (a & b) Follicular lymphosarcoma 100 mgs of ACTH daily for 10 days

no evidence of regrowth of abnormal masses within a period of 10 weeks of observation since ACTH was discontinued In the patient with Hodgkin s disease enlargement of lymph nodes occurred within 6 weeks after stopping ACTH although other lymph nodes which had previously disappeared have not reappeared during 10 weeks of observation One patient with lymphatic leukemia showed no obvious regrowth of lymph nodes for a period of 6 weeks after stopping cortisone acetate During the subsequent 4 weeks however marked enlargement of lymph nodes and enlargement of the spleen occurred This patient is receiving ACTH at the present time and involution of

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Regression of Lymphoid Tumors in Man Induced by ACTH and Cortisone*

O H Pearson L P Eliel and Rulon W Rawson

DIVISION OF CLINICAL INVESTIGATION OF THE SLOAN KETTERING INSTITUTE AND THE DEPARTMENT OF MEDICINE MEMORIAL HOSPITAL NEW YORK CITY

This study was undertaken to determine whether the rate of growth of various types of neoplastic tissue would be altered by increasing adrenal cortical function Adrenal cortical hyperfunction as manifested in patients with Cushing s syndrome is associated with a loss of body protoplasm Albright[1] has interpreted this to be the result of an inability to synthesize tissue rather than an increased rate of tissue destruction Patients with malignant lymphoid tumors were selected for study because of the observation of Dougherty and White that increased adrenal cortical function in animals resulted in an involution of normal lymphoid tissues and of Heilman and Kendall[3] that administration of Compound E resulted in regression of a lymphoid tumor in mice Studies of Dobriner and his colleagues[4 5 6] on the excretion of urinary steroids in patients with cancer including lymphoid neoplasms have revealed changes indicative of altered adrenal cortical function and these findings suggested that administration of adrenal cortical steroids or stimulation of adrenal cortical function by ACTH might influence the course of the neoplastic disease

Clinical and metabolic observations were made on 8 patients with neoplastic disease to whom adrenocorticotrophic hormone (ACTH) or cortisone acetate was administered Seven patients received ACTH (Armour) of whom 3 had chronic lymphatic leukemia and 1 each had follicular lymphosarcoma Hodgkin s disease carcinoma of the prostate and metastatic carcinoma of the breast One patient with chronic lymphatic leukemia received cortisone acetate ACTH and cortisone acetate were administered in a dosage of 100 to 200 mgm daily in 4 divided doses for periods of 18 to 30 days

* These studies were supported by grants from the U S Public Health Service the Office of Naval Research the Damon Runyon Cancer Research fund and the American Cancer Society

ACTH was stopped This patient also manifested an increase in the growth of facial hair, but no other signs of virilism were noted In one patient with lymphatic leukemia a first attack of gout appeared 2 weeks after discontinuing ACTH

In the 4 patients with lymphatic leukemia there was a marked rise in the white blood cell count during the experimental periods The initial white counts ranged from 250 000 to 750,000 with approximately 98% mature lymphocytes The white counts reached a peak after about 12 days of ACTH or cortisone acetate administration ranging from 500 000 to 1 250 000 with no change in the differential count During the remainder of the experimental period the white counts receded toward the initial level When ACTH or cortisone acetate were discontinued there was a progressive fall in the white count to below the initial level in all cases varying from 60 000 to 500 000 In none of the patients who received ACTH was there a marked change in the red blood cell count or hemoglobin level during the period of study In the patient who received cortisone acetate there was progressive fall in the red count and hemoglobin throughout the period of study and he required transfusions 3 weeks after cortisone acetate was discontinued

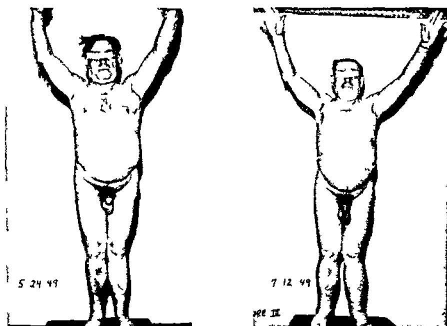


Fig 3 (a & b) Same patient as in Fig 2

lymphoid masses and spleen have occurred for a second time One patient with lymphatic leukemia showed rapid enlargement of lymph nodes and spleen within a few days after stopping ACTH After an interval of 10 weeks he is at present receiving cortisone acetate and involution of lymphoid masses has again occurred This patient will be discussed in more detail later One patient with lymphatic leukemia died 2 weeks after stopping ACTH of intercurrent infection (hemorrhagic chicken pox and bronchopneumonia) In this patient one lymph node enlarged rapidly within the first week after stopping ACTH

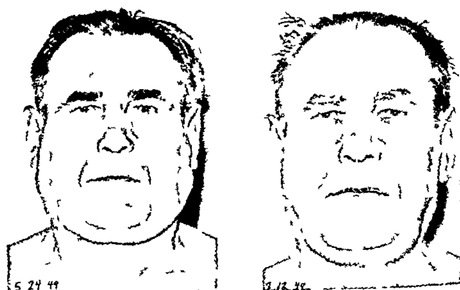


Fig 2 (a & b) Chronic lymphatic leukemia 100 mgs of ACTH daily for 18 days

None of this group of patients was critically ill at the time these studies were started All of these patients noted an increasing sense of well being during the first 2 weeks of administration of ACTH or cortisone acetate together with an increase in appetite which developed during the first week In 3 patients hunger became a major complaint After 2 weeks all of the patients noted muscular weakness which varied from mild to severe in degree During the experimental period all of the patients retained fluid and developed peripheral edema Within 24 to 48 hours after discontinuing the hormones a marked diuresis occurred and the peripheral edema rapidly disappeared In one female patient a severe acneform eruption developed on the face, arms and trunk which persisted for several weeks after

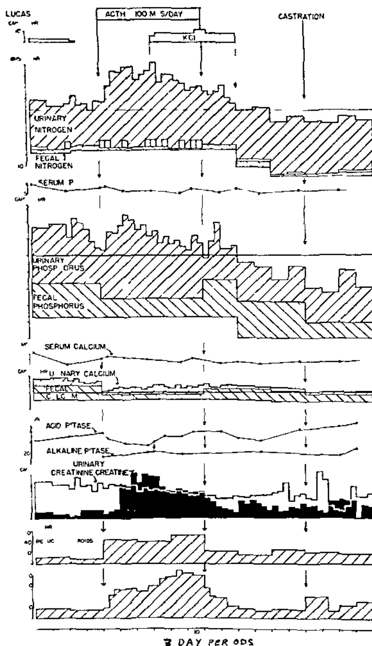


FIG 4 Balance data on patient with carcinoma of the prostate Method of plotting data is given in Reference 6

In the patients who received ACTH, there was generally a decrease in the serum chloride and potassium levels and a rise in the serum pH and bicarbonate In 3 patients the serum potassium fell to abnormal levels and characteristic electrocardiographic changes of potassium deficit developed The muscular weakness noted by these patients was probably related to the electrolyte disturbances[5] In all of the patients receiving ACTH there was a fall in the total serum proteins during the experimental period In most of these patients there was a tendency for the serum phosphorus to fall and for the fasting blood sugar to rise while ACTH was being given Glycosuria did not appear in any of these patients There was a slight decrease in the total serum cholesterol and in the cholesterol ester fraction in 4 patients in whom these measurements were made

During the experimental period all patients exhibited a negative potassium phosphorus nitrogen and calcium balance and a positive sodium and chloride balance In the 6 patients with lymphomatous lesions the excretion of phosphorus during the administration of ACTH or cortisone acetate was greater than the phosphorus excretion calculated from the actual nitrogen and calcium excretion using the accepted ratios for N to P in protoplasm and Ca to P in bone[6] Chemical analysis of fat free muscle and tumor tissue from 3 patients (2 with lymphatic leukemia and one with follicular lymphosarcoma) revealed 2 9 times as much phosphorus per unit of nitrogen in tumor tissue as in muscle tissue These data provide evidence that tumor tissue was actually destroyed in this group of patients (Figs 4 5 6 7)

In one patient with lymphatic leukemia the dietary intake was doubled after 18 days of ACTH administration and ACTH was continued for an additional 12 days This increase in diet was associated *with a sudden shift from a negative to a positive nitrogen* balance When ACTH was stopped there was a rapid increase in the size of the lymphoid masses as well as the spleen in this patient This data indicates that the metabolic response induced by ACTH may be altered by the dietary intake and appears analogous to the results of similar experiments by Ingle[7] in rats

Steroid studies on these patients were carried out by Dr Dobriner and his colleagues and were discussed by Dr Dobriner yesterday

The excretion of ketosteroids and reducing steroids was increased in all patients during the administration of ACTH There was considerable individual variation in the extent of this steroid increase and in 2 patients a significant increase was observed only after the dosage of ACTH was increased from 100 to 200 mgm per day

Histological examination of lymph nodes before and after ACTH or cortisone acetate was made in 2 patients with lymphatic leukemia and in 1 patient with follicular lymphosarcoma There was no

Fig 6 Balance data on patient with chronic lymphatic leukemia

Fig 7 Continuation of data in Fig 6

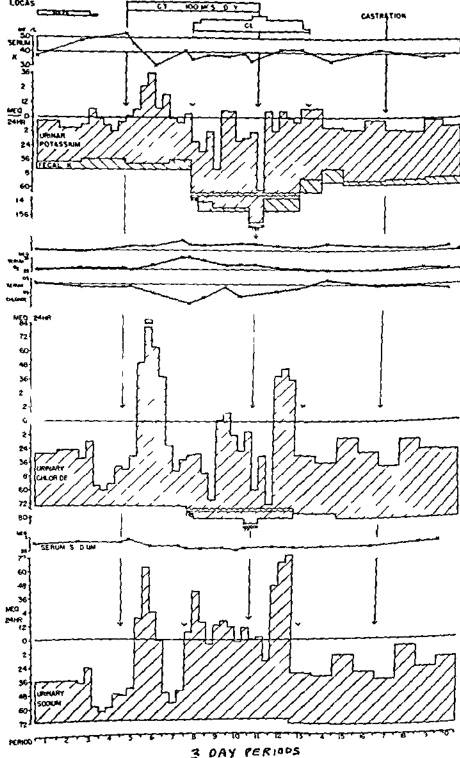


Fig 5 Continuation of data in Fig 4

tion, interpretation, and presentation of data pertaining to metabolic balances notably those of calcium, phosphorus, and nitrogen *J Clin Endocrinol*, 5 367–395 1945

7 Ingle D J Some studies on the role of the adrenal cortex in organic metabolism *Ann New York Acad Sc* 50 576–595, 1949

DISCUSSION

DR HARRY SHWACHMAN We are treating 2 patients with acute lymphatic leukemia in childhood with ACTH They are both being given the material at the present time so it is too early to draw conclusions but so far we have noted a marked diminution in the size of the spleen in one patient a decrease in the number of blast cells in the peripheral blood from about 40% down to about 8% and also a concomitant increase in the percentage of mature neutrophils with a stimulation of the erythropoietic tissue, so that we have a rise of the reticulocytes to about 19% with a marked increase in the number of nucleated red cells in the peripheral blood

I wonder if anyone has observed this erythropoietic stimulation in the use of ACTH?

DR O H PEARSON We have 2 patients in whom there seems to have been an increase in red blood cell count and hemoglobin level I didn t want to discuss it because it is detail but there has been a definite rise in 2 patients which looks suggestive of improved erythropoietic activity

DR ROBERT KLEIN I can verify that In the newborn child when given whole adrenal extract the number of nucleated red cells increases dramatically We believe that this is the common mechanism in newborn diseases

DR JAMES J SMITH I would like to ask Dr Pearson if he has noticed any changes in head hair distribution following ACTH The pictures of the individual who was given at full length seemed to me to show a diminution of head hair I wonder if that is merely photography?

DR O H PEARSON We had one girl who developed this severe acne and increase in facial hair The hair on the top of her head is falling out It is not a localized alopecia but a localized falling of hair It looks as though she is developing a temporary receding hair line

VOICE Will you say something about the changes in bone marrow?

DR O H PEARSON There were no changes in the bone marrow we are talking about

definite change in the histological picture of the nodes in the patients with leukemia In the lymph node obtained from the patient with lymphosarcoma following ACTH administration there was a disappearance of germinal centres and a decrease in cellularity

In none of the patients studied has a complete clinical remission of the disease been obtained These observations were designed to be short term metabolic studies to determine whether alteration in adrenal cortical function would affect the rate of growth of tumors Although no obvious clinical response was observed in the 2 patients with carcinoma it cannot be concluded that ACTH administration was entirely without effect on the growth of these tumors since assessment of tumor growth in these patients could only be made by indirect means The possible role of ACTH and cortisone acetate as therapeutic agents in patients with lymphomatous tumors has not been established by these studies It remains to be determined whether complete clinical remissions can be obtained by more prolonged administration of these hormones It is of interest that 2 patients with lymphatic leukemia have shown a second response to the administration of ACTH or cortisone acetate indicating that tumor resistance has not yet developed to these agents

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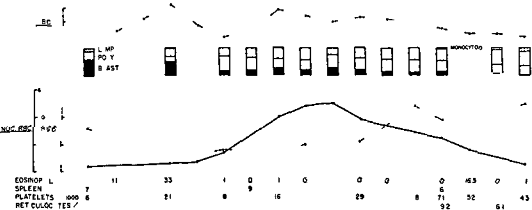
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6 Reifenstein E C Albright F and Wells S L The accumula

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NUC RBC
EOSINOP L
SPLEEN
PLATELETS 1000
RET CULOC TES

Fig 1

26

The Effect of ACTH in Acute Leukemia in Childhood*

Sidney Farber Harry Shwachman Rudolf Toch, Virginia Downing B Hughes Kennedy John Hyde

BOSTON CHILDREN S HOSPITAL HARVARD MEDICAL SCHOOL D ta from the Tumo Chemotherapy Sect on of the Boston Ch ld en s Hospital

A boy 5¾ years of age whose symptoms began in January of 1949 with pallor and poor appetite was admitted on February 27, 1949 to the Children s Medical Center with a white count of 4200 55% of which were blast forms The bone marrow contained 98% blast forms

Between February 27, 1949 and October 11 1949 treatment included folic acid antagonists which did not produce a remission

At the time ACTH was begun on October 11, 1949 the child was in complete relapse

October 11, 1949 Started on ACTH, Lot #H3706 50 mg daily Weight at that time 33¼ pounds Hepatosplenomegaly of 2 and 7 cm respectively Some bleeding from his mouth Poor appetite Pain in arms and legs Hemoglobin 7 9 gm , white count 5 500 with 52% blasts platelets 21 000, eosinophils 33 per cu mm Blood sedimentation rate 30 mm per hour, Wintrobe method Eosinophils dropped to 11 per cu mm by the following day Bone marrow showed 53% blasts and 10% erythroid cells ACTH continued until October 20 1949 a total of 500 mg intramuscularly (Fig 1) Weight at the end of that period was 37 pounds Some obvious evidence of ascites was present but there was also some definite tissue gain White count had been essentially the same during that period but there had been a moderate drop in blasts Two days after cessation of therapy blasts numbered only 4% Platelets had risen to a maximum of 118 000 but dropped to 52 000 on the day after cessation of therapy Reticulocytes reached 19 2% Eosinophils varied between 0 and 11, and rose to 16 on the day after treatment was stopped Blood sedimentation rate

* Post-conference follow up of acute leukemia case presented at conference

27

Effect of ACTH in Certain Types of Malignancy

S G Taylor III and Roger S Morris Jr

PRESBYTERIAN HOSPITAL AND UNIVERSITY OF ILLINOIS MEDICAL SCHOOL CHICAGO

ACTH has been administered to the following patients with malignant disease

Advanced carcinoma of the breast with metastases	2 cases
Mycosis fungoides	1 case
Carcinoma of the trachea	1 case
Ewing s tumor	1 case

Of the two patients with carcinoma of the breast one appears clinically to show an acceleration of the disease The other patient experienced a prompt reduction of fever healing of a carcinomatous ulcer and temporary improvement in appetite However palpable nodes increased in size and after 10 days of clinical improvement her condition worsened rapidly At autopsy neither case showed any evidence of regression of tumor

A 61 year old man with a squamous cell carcinoma of the trachea which had been treated with irradiation and repeated bronchoscopic resections for 6 years developed severe respiratory obstruction requiring bi weekly bronchoscopic intervention to maintain an adequate airway He was treated with radon seed implantation nitrogen mustard and further roentgen ray therapy Three weeks after the last of these forms of therapy there had been no improvement ACTH was instituted An airway has been maintained adequately without further broncho copic intervention for 12 weeks during which time he has received ACTH Healing occurred at the site of the lesion The patient developed fat pads and facies suggestive of Cushing s syndrome This regressed following reduction of the dose Metabolic effects are shown in Fig 1

A 16 year old boy who has Ewing s tumor with extensive metastases has shown remission of fever some relief of pain freedom from nausea and vomiting marked increase in appetite necrosis and some regression of metastases and marked myeloid and erythroid stimula

dropped to 0 corrected Wintrobe method Temperature was normal There was no further bleeding The hemoglobin had risen spontaneously to 10 gm A bone marrow aspiration done at the conclusion of therapy showed 37% blasts and 33% erythroid activity Nine days after therapy stopped on October 29 the child weighed 42 pounds The spleen was now 1 cm below the costal margin and the liver was no longer palpable The child was eating ravenously and feeling exceedingly well

Nov 4 1949 The child weighs 43 pounds There is no longer any evidence of ascites Appetite continues to be excellent

Nov 7 1949 Bone marrow aspiration was repeated, showing definite evidence of remission The child had a white count of 5 700 Reticulocytes 4% Platelets on November 2 were 66 000 Blood sedimentation rate however had risen to 22 mm per hour corrected Wintrobe method

Nov 16 1949 Continues in excellent clinical condition Physical examination shows no abnormality Hemoglobin and red count normal (13 6 gm and 3 9 million) Platelets on November 9 were 235 000 and today are 126 000 White count today 5,500 Differential count was normal

Dec 30 1949 The boy is still clinically and hematologically in remission

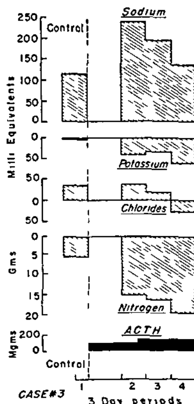


FIG 2

catatonia in another Regression of these symptoms promptly followed reduction of dose

In no patient with the exception of the one with mycosis fungoides can any regression of the disease be attributed to ACTH alone

DISCUSSION

DR CHARLES D BONNER We treated 2 patients one a 19 year old man with Hodgkin s disease and a second who was a 58 year old man with neurogenic sarcoma of the kidney with metastases to the liver

First the Hodgkin s disease patient had been treated for several years with nitrogen mustards and his last recurrence was several months ago He was left with cerebellar findings of nystagmus and ataxia He was not able to walk alone and was not able to read a newspaper Following some local x ray therapy to the cerebellum he did get to the point where he could read large headlines in the news paper and his condition became stationary for a long period of time

We gave him 50 mgs a day of ACTH (Armour) and continued for

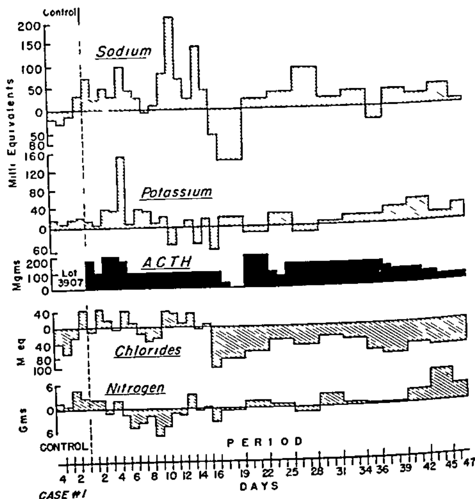


FIG 1

tion during 21 days of ACTH therapy An unusually large urinary nitrogen excretion has occurred as demonstrated by Fig 2

No evaluation of the ACTH on the tumor can be made

Marked clinical improvement has occurred in a patient with extensive mycosis fungoides of 6 years duration She has been given 2,462 mg of ACTH over a period of 27 days No new lesions have appeared Epithelization of the old lesions has occurred and is still in progress Itching previously only partially controlled by heavy sedation disappeared after 4 days of treatment Histologically the disease is still present and active

Fig 3 shows the metabolic changes

In four of the patients treated, unusual mental symptoms developed These consisted of a hypomaniac state in two, a paranoid reaction with disorientation in one and a schizoid reaction with

I still am not quite sure whether the drop in requirement for narcotics was due to the ACTH During his psychotic episodes he believed that his pain was due to gas and that by means of rectal tubes he could control his pain A small rectal tube gave relief for 2 hours a middle sized tube for 3 hours and a big one for 5 hours

DR ARTHUR J MERRILL I would like to ask if there is any possible relationship of these mental symptoms to potassium deficiency We have seen the same thing occur in patients with renal disease with potassium deficiency

DR WALTER BAUER I would hate to hazard a guess in that regard I don t think it is quite necessary or quite that simple I don t know how Dr Thorn and some of the others feel about it I think that would be making it a little too simple from the observations that we and others have made because certainly you can t correlate dramatic states which we have seen with that in all instances

DR S G TAYLOR III Serum potassium did not drop in this patient but she had had a very heavy potassium excretion and sodium retention Potassium was administered but no improvement occurred in the mental status

DR FREDERIC C BARTTER We have been looking for an index of changes in tumor tissue as opposed to other types of tissue in metabolic experiments We thought that in a patient with very extensive bone metastases from a carcinoma of the breast the calcium excretion might provide such an index if the metastases were caused to diminish in size more calcium should go into bones and less be excreted

Fig 4 shows the effects of ACTH on Ca (and N P and K) metabolism in such a patient Note that the extremely high urinary Ca (from 560 to 800 mgm a day) was brought down to the normal range with ACTH and that it remained low throughout the experiment

We are by no means ready to say that this was due to regression of tumor tissue However this patient did have an external ophthalmoplegia on the right which improved distinctly and almost disappeared on ACTH and eventually she was autopsied and it was shown that the ophthalmoplegia was due to tumor tissue in the meninges in the right superior orbital fissure

DR S G TAYLOR Our breast cancer cases were both very far advanced One had metastases in the liver and the other had extensive metastases throughout the lung the brain and the abdomen

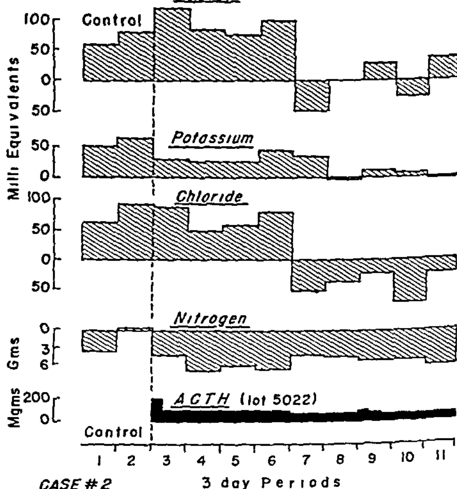


FIG 3

30 days All we can say is that by the end of that time starting at about the second week he was able to read fine print in the news paper but he still wasn t able to walk any better There was no re gression of the size of his spleen but immediately following the course of ACTH he was relapsing into another acute phase of Hodgkin's disease

As far as the neurogenic sarcoma of the kidney is concerned this patient had a massive hard nodular liver with positive biopsy He was requiring large amounts of demerol for severe pain All we can say again is that requirements for narcotics dropped but about the tenth day he had a marked paranoid reaction which remained even after the drug was withdrawn

He had received 100 mgs ACTH (Armour) a day for 30 days and

I still am not quite sure whether the drop in requirement for narcotics was due to the ACTH During his psychotic episodes he believed that his pain was due to gas and that by means of rectal tubes he could control his pain A small rectal tube gave relief for 2 hours a middle sized tube for 3 hours and a big one for 5 hours

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DR S G TAYLOR Our breast cancer cases were both very far advanced One had metastases in the liver and the other had extensive metastases throughout the lung the brain and the abdomen

The use of ACTH in further investigation in carcinoma of the breast should be tried in patients in whom the disease is not so far advanced These were very late cases One patient was nearly moribund

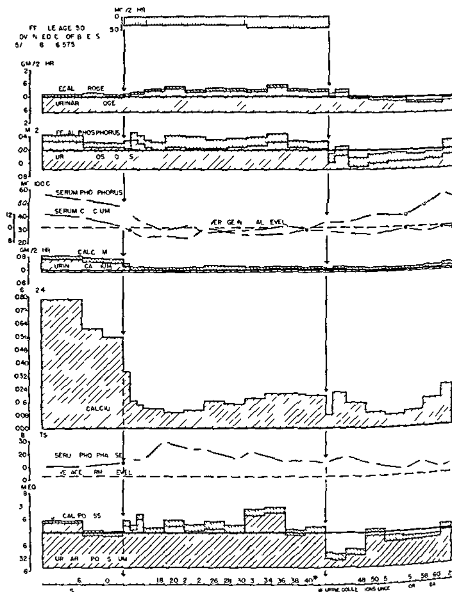


Fig 4 Patient R H M C H #615754 female 50 with advanced carcinoma of breast Nitrogen phosphorus, calcium and potassium balances and serum P, Ca and alkaline phosphatase during ACTH therapy

28

Changes Produced by the Administration of ACTH and Cortisone in Rheumatoid Arthritis

W S Clark Marian W Ropes and Walter Bauer

MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

To date we have treated only 4 patients with rheumatoid arthritis

The first patient received cortisone for 12 days during which time detailed metabolic studies and other observations were made

The second patient has been on the metabolic ward the past year While on a constant regime he has received testosterone cortisone desoxycorticosterone glucoside desoxycorticosterone glucoside and cortisone and ACTH The detailed acid base balance studies done during these months will be reported by Dr Ropes when Dr Sprague s findings are discussed

The third patient is being studied on one of the medical wards In this instance we shall attempt to determine the effect of ACTH therapy on the inflammatory process the synovitis We obtained a generous biopsy from the left knee prior to instituting therapy and will do a second biopsy on the same articulation when the knee has returned to normal or a stationary state as judged by palpation and repeated synovial fluid analyses

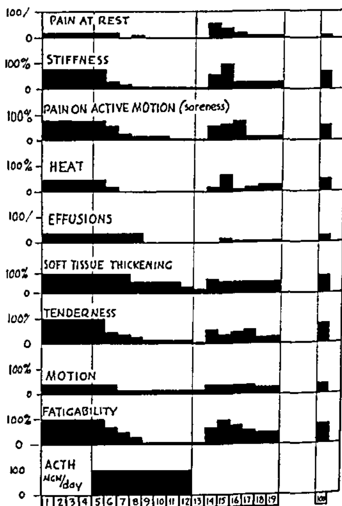
The fourth patient is suffering from rheumatoid arthritis and severe exfoliative psoriasis She has been good enough to permit daily skin biopsies—a total of 15 have been done thus far Though the erythema and scaling have diminished, no demonstrable histological alterations have been observed during the first 12 days of therapy

I shall make no attempt to give a word description of what happens to patients with rheumatoid arthritis when receiving either cortisone or ACTH as this has already been done in a most masterful manner by our friend Phil Hench and has been depicted in a most striking manner by his movies

The effect of cortisone and ACTH on the clinical manifestations

of rheumatoid arthritis has been essentially the same in each of the patients we have treated Fig 1 depicts the effect of ACTH in doses of 100 mgm per day on each of the articular manifestations of patient M M It will be noted that the improvement observed during the 8 days of therapy persisted for an additional 24 hours Following the completion of the metabolic study the only medication the patient received was aspirin

Fig 2 shows the effect of cortisone desoxycorticosterone glucoside

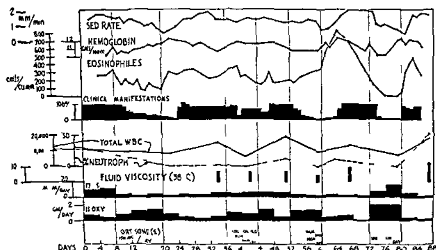


MM ♂ 43 Rheumatoid Arthritis Effect of ACTH on Clinical Manifestations

DIET FLUID INTAKE AND WEIGHT CONSTANT

Fig 1

cortisone and desoxycorticosterone glucoside and ACTH on the sedimentation rate hemoglobin eosinophil count composite clinical manifestations synovial fluid (total leukocyte count neutrophil count and viscosity) 17 ketosteroid and 11 oxysteroid excretion of patient M M The changes which took place during each therapeutic period are readily apparent The observed clinical improvement was approximately of the same magnitude in each instance except for the very questionable effect during the administration of desoxycorticosterone glucoside The graph following the ACTH treatment period



MM 554400 ♂ Wt 70 KG Moderately Severe Rheumatoid Arthritis Duration 10mos All Peripheral Joints involved Anorexia Wt loss Fatigue Vasomotor Symptoms Lymphadenopathy Sq nodules Hepatomegaly

— DIET FLUID INTAKE AND WEIGHT CONSTANT —

FIG 2

should be pushed to the right one day because the rebound did not take place until the second day post therapy

Slight synovial fluid changes occurred during each treatment period These were slight as compared to those observed in patient J A

In patient M M heat pain perception levels were measured by Dr W P Chapman during the time between the periods of treatment with desoxycorticosterone glucoside cortisone and desoxycorticosterone glucoside and with ACTH The heat levels causing pain are expressed in gm cal / sec / cm the mean value for each test being represented by the black dot and the range for that test by the open circles During or for the two days following treatment with all three

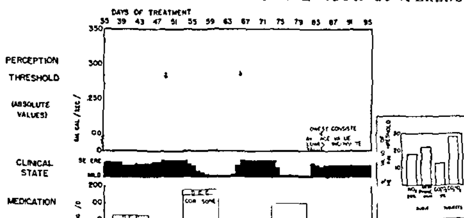


FIG 3 Heat pain perception levels during treatment with Compound F D C C and ACTH

J A 21YR ♀ Moderately Severe Rheumatoid Arthritis—
7 yr Duration Weakness Fatigability, Wt Loss Vasomotor
Symptoms Generalized Arthritis 2 yr Remission-1944 to 1946
Arthritis Progressive Since Then

FIG 4

agents there was a greater variability in the amount of heat causing pain Elevations in the threshold levels were more striking than decreases in these levels The magnitude of these changes was somewhat less than that obtained with known analgesic agents as shown at the right of the figure Studies are now in progress to determine whether the variations in the heat pain threshold can be consistently obtained in conjunction with steroid therapy and whether these changes are

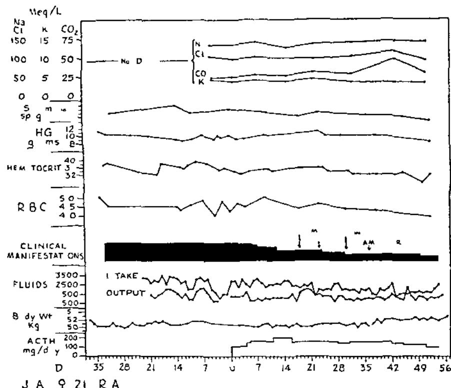


FIG 5

sufficiently pronounced to help explain the effects of these agents on clinical pain

In Fig 4 are recorded some of the observations made on the individual on whom we did the biopsy of the knee It will be noted that her rheumatoid arthritis was relatively stationary until treatment was started It was necessary to go as high as 200 mgm of ACTH per day before obtaining the desired effect on the clinical manifestations of her disease

During the third week of treatment, the patient began to exhibit

features not unlike those seen in Cushing s disease hirsutism acne moon face and finally amenorrhea

The alterations which took place in the synovial fluid were striking The initial fluid had a cell count of 10,200 41% polymorphonuclears a lower synovial fluid sugar than the serum and a viscosity of only 20 With treatment the sugar returned to normal, the cell count fell to 150 the polymorphonuclear count was normal, and the viscosity had risen to 301 The mucin precipitated normally Un

J A ♀

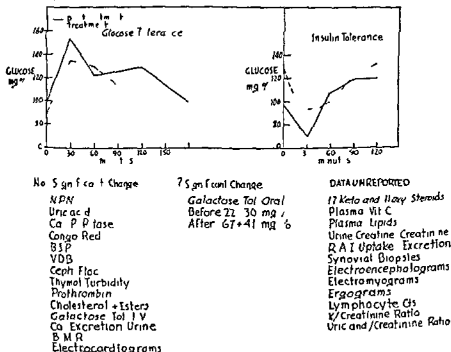


FIG 6

fortunately the amount of fluid obtainable was too small to enable us to determine its mucin content

Fig 5 shows the effect of ACTH administration on four of the serum electrolytes The rise in CO was not accompanied by a fall in the serum potassium as is usually the case The other findings I need not comment on

In Fig 6 are listed the other studies that were done on J A and the other rheumatoid arthritics There was only a slight effect on the glucose tolerance curve the same was true of the insulin tolerance test There were no significant changes in any of the tests recorded in the first column though we have seen changes in the electrocardiograms (T waves) of other patients



Fig 7

Whether or not the oral galactose tolerance test changes are significant we do not know

The electroencephalograms have not been interpreted In another patient following cessation of cortisone therapy the alpha waves that had been present in the temporal region disappeared

The electromyographic and ergographic tests done simultaneously show much longer and better sustained work load than before treatment

Figs 7, 8 and 9 illustrate the florid synovitis present in the left knee of patient J A prior to institution of ACTH treatment In Fig 7, the typical changes including a lymphocytic nodule are readily seen Fibrinoid change is present in Fig 8 and characteristic palisading in Fig 9

Fig 10 illustrates the flexion deformities of the fingers of patient



Fig 8

J A which we thought were due to peri articular fibrosis They had been present for two plus years Though we did not expect them to be favorably affected one notes in Fig 11 after treatment, passively these fingers could be brought to 180 degrees though the patient herself could not do it

Fig 12 is a photograph of patient J A before treatment

Fig 13 shows the moon face and hirsutism of patient J A on ACTH treatment The side view (Fig 14) illustrates the beard present at the same time

I will say nothing more about ill effects until we present our findings on idiopathic ulcerative colitis

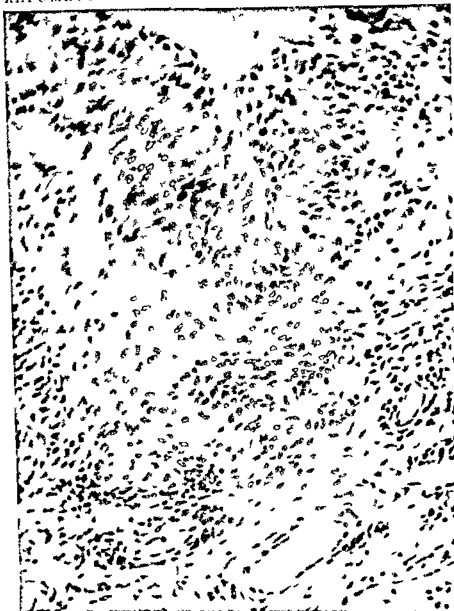


FIG 9

DISCUSSION

DR MARIAN W ROPES I would like to discuss the electrophoretic changes observed in two patients, M M and R M (See Fig 15)

The heavy line represents the serum electrophoretic pattern the

dotted line the joint fluid the straight line at the top or bottom in each case being the normal

One notes that in all the treatment periods in patient M M the albumin rose except with desoxycorticosterone With cortisone and desoxycorticosterone glucoside and with ACTH, it rose but fell after each treatment The joint fluid also showed an increase in the albumin content and it remained higher at the end than at the beginning of treatment The other changes are slight Desoxycorticosterone alone did nothing to the electrophoretic pattern Alpha 1 globulin dropped on cortisone cortisone and desoxycorticosterone and ACTH Alpha 2 globulin dropped slightly after treatment with cortisone on cortisone and desoxycorticosterone it dropped definitely, and on ACTH it dropped slightly



Fig 10

The change in beta globulin is probably insignificant since the concentration seems to vary

Gamma globulin concentration dropped very definitely, and in this case it did not return to its original level and at the end of treat

ment was lower than at the beginning The changes in the joint fluid are somewhat comparable throughout

The other patient (R M) studied on the metabolic ward had less marked changes The pattern was not so abnormal to begin with and there was very little change in the period of 12 days of treatment with cortisone The gamma globulin in his fluid actually rose the significance of which we do not know

Serum albumin was low in both of these cases as it always is in moderately severe rheumatoid arthritis



Fig 11

DR R LEVINE (Michael Reese Hospital Chicago) I would like to say that the group at Michael Reese Hospital where we have had the experience of treating two cases with cortisone for rheumatoid arthritis confirms almost all details of what Dr Bauer has just said

I would like to remark on one or two things One is that just as he did we found in one case in a woman the necessity of giving 200 mgs a day of cortisone before clinical improvement started after ineffective use for a week of 100 mgs a day

The second thing is that in two cases with ACTH that were improved in the hospital and then sent out on chronic therapy with re

duced dosage of ACTH they are well maintained clinically only if some acne and some edema is present In other words, the effective so called maintenance dose and the side reaction dose, are very close to each other



Fig 12



Fig 13



Fig 14

Our general conclusion after extensive metabolic and endocrine testing is that these patients do not seem to suffer from any presently detectable endocrine dysfunction We are most impressed with the striking effects of cortisone upon the psychological behavior of the patients and the rapidity with which 'stiffness and pain are relieved Those aspects are being subjected to detailed study

DR C H TRAEGER I would like to ask Dr Bauer and any of the other folks who have been using ACTH in rheumatoid arthritis whether or not they have ever encountered one of two things which we have encountered in instances among 14 patients

First, an adrenal escape during treatment followed by a complete collapse of the remission with complete return of all symptoms

DR WALTER BAUER On what dose?

DR C H TRAEGER 100 mgs 25 times 4 Second whether or not any patients have been encountered by anyone who could not tolerate ACTH even in small doses

We have had one case that went through rather a stormy febrile session following ACTH and one who went into shock following only 9 mgs of ACTH

Have those experiences been observed by anyone else?

DR CHARLES RAGAN Two serological reactions seen in rheumatoid arthritis—the agglutination of group A hemolytic streptococci and of sensitized sheep cells—have been observed in 8 patients with rheumatoid arthritis treated with ACTH (Armour) These patients were treated for varying lengths of time—six for 7–10 days patient A A for 27 days and patient M M for 4 months In all these patients the usual criteria for clinical improvement appeared during the administration of ACTH Sedimentation rate fell and serum globulin when elevated fell to normal levels The streptococcus agglutination remained very constant (Fig 16) In one patient a positive agglutination became doubtful This patient will be discussed in detail by Drs Hoefer and Glaser in their paper on mental and electroencephalographic changes She developed an acute mania while on ACTH and arthritic symptoms failed to reappear while the mania continued Subsequently following cessation of the mania symptoms recurred and the streptococcus agglutination is again positive

Sensitized sheep cell agglutinating titer remained constant save in the two patients treated for longer periods (See Fig 16) In both of these there was a significant drop in titer which however never fell to normal levels—below 16 In our experience these two serologi

BUMIN / 60 40

2 α / 0

2 α_2 /

2 β /

2 γ γ

gm %

ns 0

E DCG E DCG ACTH

0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88

DAY

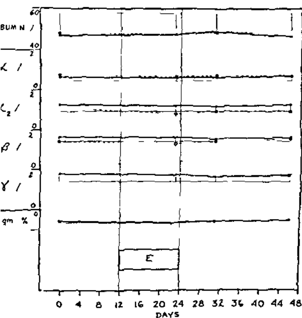


FIG 15

cal reactions have in most instances remained unchanged during treatment with ACTH This is in contrast to other more non specific protein reactions such as the sedimentation rate hyperglobulinemia and an occasionally positive cephalin flocculation which revert to normal with ACTH therapy This finding suggests that these two serological reactions may represent an integral part of the disease rather than the host response to the disease which latter is modified by the administration of ACTH

Patient	*	Streptococcus Agglutination result	highest titer	first tube	Sensitized Sheep Cell Agglutination
W O'T	1	negative	0	0	16
	2	"	0	0	32
P F	1	positive	1/640	++	64
	2	"	1/640	++	32
M G	1	positive	1/640	++	16
	2	doubtful	1/160	±	32
A A	1	positive	1/320	++	512
	2	"	1/160	++	32
M M	1	positive	1/320	++	512
	2	"	1/320	++	64
E E	1	positive	1/320	++	256
	2	"	1/320	++	1024
N M	1	positive	1/640	++	32
	2	"	1/640	++	16
G McS	1	doubtful	1/80	±	128
	2	"	1/80	±	64

* 1 Control
2 During treatment

Fig 16

DR JEROME W CONN I would like to emphasize one point that Dr Bauer went over rather rapidly It was his finding that the mucin content of the joint fluid precipitated normally after ACTH

I would like to tell you about one case that Dr Robinson of our Arthritis Unit and I have studied This patient was given 100 mgs of ACTH daily The pre ACTH joint fluid had a white count similar to

Dr Bauer's, a little over 10 000 On the third day the count was 500 and on the fifth day there wasn t any more fluid

While the mucin precipitation test was grossly abnormal before ACTH, after 3 days of ACTH when fluid was still available, the mucin polysaccharide precipitated by Dr Bauer s test perfectly normally The ability of the arthritic to make a longer chain polysaccharide may be a very fundamental point in the study of the effectiveness of ACTH and Compound E in this disease

DR WILLIAM Q WOLFSON The Michael Reese Rheumatoid Arthritis Research Group* has been interested in the correlation of clinical improvement, decrease in sedimentation rate and regression of abnormal serum protein changes during remissions induced by Cortisone or by ACTH because of the possibility that such correlations might point toward the mechanism of action of these substances Observations during chronic ACTH administration have been made on two patients with typical rheumatoid peripheral polyarthritis, on one patient with psoriatic arthritis and on one patient with disseminated lupus erythematosus In these cases both Westergren and Wintrobe sedimentation rates were followed and frequent serum protein fractionations were performed by a chemical method[1] which gives results comparable to those of electrophoretic analysis

Fig 17 summarizes data from one of the patients with rheumatoid arthritis and from the patient with disseminated lupus erythematosus The findings in the two patients not illustrated were similar The typical abnormalities present before ACTH was given were elevated sedimentation rates, low serum albumin concentrations, high serum alpha globulin concentrations and high serum gamma globulin concentrations In the regression of these findings when ACTH is given, the first change has been an increase in the ratio of serum albumin to serum total globulin (true A/G ratio) This change derives from a simultaneous increase in albumin values and decrease in the two elevated globulin fractions The change in the ratio of serum albumin to gamma globulin was approximately parallel, but was most marked during improvement in the patient with disseminated lupus erythematosus Because the albumin values found by the Howe method include both true albumin and alpha globulin similar rapid changes in A/G ratio cannot be expected from this method

Clinical improvement and improvement in serum protein patterns have been much more closely associated than have clinical im

* The Michael Reese Rheumatoid Arthritis Research Group includes Drs Samuel Sorkin (Chairman) Clarence Cohn Roy Grinker Henry S Guterman Louis N Kat Rachmiel Levine Edward F Rosenberg Karl Singer Harry F We sberg and William Q Wolfson

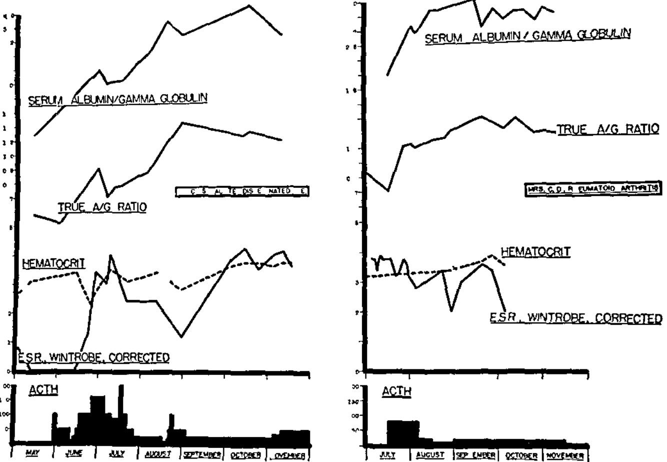


Fig 17 *Changes in serum protein pattern sedimentation rate and hematocrit during chronic administration of ACTH in a patient with disseminated lupus erythematosus and a patient with typical rheumatoid polyarthritis*

provement and decrease in sedimentation rate Each patient has shown a more or less prolonged period in which a relatively normal serum protein pattern coexisted with an erythrocyte sedimentation rate value which was little lower than that obtaining before ACTH was begun Similarly a serious clinical relapse in one of the patients with rheumatoid arthritis was accompanied by a regression in serum protein pattern

An unusual finding was that of very low sedimentation rates in the patient with disseminated lupus early in treatment and at a time when she appeared clinically moribund Because fibrinogen values were not obtained any explanation must be conjectural A plausible interpretation in the light of present knowledge of the determinants of sedimentation rate is that hypofibrinogenemia due to liver damage may have been present at the height of the illness This suggestion is consistent with the presence of an enlarged tender liver which was palpable throughout the first few months of ACTH administration and with the extremely hemorrhagic character of her skin lesions, which coexisted with a normal capillary fragility as determined by the Eddy Dalldorf procedure

The impression has been gained from studies by other investigators that an elevation in sedimentation rate is the most sensitive indicator of disease activity in rheumatoid arthritis Robinson and his associates studied sedimentation rates and electrophoretic protein partitions in patients whose clinical condition suggested early rheumatoid arthritis They found that in those patients in whom typical rheumatoid arthritis later developed the most consistent laboratory abnormality was an elevation in sedimentation rate most often associated only with an elevation in plasma fibrinogen Less often, other significant electrophoretic abnormalities also were present

The impression gained from the study of ACTH induced remissions is consistent with these observation An elevated sedimentation rate appears to be a much more sensitive and persistent indicator of disease activity than is any abnormality in the serum protein fractionation pattern Apparent clinical well being and normal serum protein patterns may in fact, coexist with sedimentation rates as high as those present before treatment On the other hand the finding of serum protein patterns which are returning to normal may give objective evidence of increasing control of disease activity long before this fact could have been established by study of the sedimentation rate

REFERENCE

1 Wolfson W Q, Cohn C Calvary L and Ichiba F Studies in serum proteins V A rapid procedure for the estimation of total

protein true albumin total globulin alpha globulin beta globulin and gamma globulin in 1 0 ml of serum *Am J Clin Path* (Technical Section) 18 723 1948

DR DAVID MARKSON (Wesley Memorial Hospital Chicago) I would like to ask Dr Bauer a question about sensitivity to ACTH

We have had one patient to whom we gave ACTH and immediately we got a reaction The third day she developed a generalized urticaria and neurotic edema

Secondly I would like to ask Dr Bauer how he uses these patients For example the advance arrested rheumatoid arthritic who had his arthritis say for 20 years How much of the process of the rheumatoid arthritis is reversible? How do you choose?

DR CURRIER MCEWEN (New York University New York City) Dr Bauer we have been surprised to find in one patient in whom subcutaneous nodules were removed at intervals that although the nodules became very much smaller after ACTH was begun histological study revealed no changes either in the number and types of cells found or in the general topography This observation fits in with what Dr Pearson reported in regard to lymphomatous tumors but it does not coincide with the changes in synovial biopsies which Dr Hench showed us several months ago I wonder what the experience of others has been in this connection?

DR C TRAEGER Dr Bauer have you observed any of the escape phenomena mentioned earlier by Dr Adams?

DR WALTER BAUER To answer Dr Traeger we have not seen an escape of the type he has described I think most of us have seen minor escapes as shown by an increase in eosinophils or symptoms To date we have not seen anyone who could not tolerate the drug nor have we seen anyone with sensitivity of the type described by Dr Markson However we have treated only 5 people with ACTH

I wish to call attention to one thing which I failed to mention namely that the administration of desoxycorticosterone did not increase the symptoms of the patient with rheumatoid arthritis

I agree with what Dr Conn says about synovial fluid It is very exciting to know that with the administration of ACTH the synovial fluid can return to normal particularly the polysaccharide contained therein

As regards pathology we have one patient in whom we excised symmetrical olecranon nodules the second nodule was removed 14 days after a 12 day period of cortisone therapy There was no demonstrable difference in the histology pre and post treatment

What Dr McEwen says about nodules is not surprising I don't know that I agree with everything that Dr Wolfson said about sedimentation rates but time will not permit us to continue the discussion

I would like to say a few words about the action of these hormones in rheumatoid arthritis To use a crude simile, active rheumatoid arthritis can be thought of as a Bunsen burner The burner is going full tilt when you introduce cortisone or ACTH when it turns off however the pilot light remains on As soon as you discontinue hormone therapy the Bunsen burner is in full flame within a few days From our experience in treating patients to date, we must conclude that the disease mechanism remains active and the X agent that causes it is not eradicated

DR C H TRAEGER In discussing the use of ACTH in rheumatoid arthritis we have experienced several untoward reactions

Febrile Reaction

1 J C age 49, was given an initial dose of 10 mgs ACTH (Armour Standard) Within 4 hours, malaise chills, headache and chest pain were noted and his temperature rose to 104° F There was no rise in WBC count Five days later 10 mgs ACTH (Armour Standard) was again injected A similar reaction with temperature 104° F and no increase in leucocytes followed Skin tests showed no allergy to ACTH

Anaphylactoid Reaction

2 A N age 22 in July 1949 received small doses of ACTH of low potency with much posterior pituitary material This was discontinued because of complaints of headache dizziness and diplopia Three months later 9 mgs ACTH (Armour Standard) was injected Within a minute following this small dose she complained of burning sensation of hands feet and all mucous membrane lined orifices Cutaneous erythema appeared which quickly gave way to extreme blanching, respirations were 60 per minute pulse was 160 The blood pressure, normally 110/60 dropped within 2 minutes to 80/60 and in 4 minutes to 60/40 During this period the patient had an involuntary bowel evacuation and complained of intestinal cramps At this time and for the following 4 hours she had several episodes of projectile vomiting Atropine demerol and ephedrine were administered intramuscularly Within 30 minutes the respiratory rate returned to normal The blood pressure and pulse returned to the preinjection level within 6 hours The patient did not lose consciousness at any

time She complained of feeling weak and was prostrated throughout this period

Five hours after the injection of ACTH she developed an angioneurotic edema of the lower lip and chin For 24 hours she complained of pruritus and burning of the palms and soles

There was no history of allergy Intradermal tests with ACTH 1 10 000 dilution resulted in a severe and almost instantaneous skin reaction, manifested by wheal, pseudopodia and surrounded by erythema Pork extract 1 500, was well tolerated intradermally

ACTH of the same lot number had been administered frequently to other patients without untoward effects indeed from the same vial used in this patient 10 mgs had been withdrawn just previously and injected into another patient without untoward reaction

Allergic Reaction

3 M H, age 34 for 35 days during July and August received ACTH of low potency with an early adequate eosinophile response which later failed to occur Clinical response was classified as fair after 3 days administration because of the occurrence of blotchy red pruritic areas suggesting urticarial reactions at the site of each injection These disappeared after antihistamine medication Injections of ACTH were resumed without recurrence of this phenomenon

Two months following the cessation of this course of ACTH injections this hormone was again injected intramuscularly in a dose of 5 mgs (Armour Standard) Within 10 minutes she complained of generalized burning and itching followed by widely distributed urticaria These changes responded satisfactorily to antihistamine drugs There was a marked reaction to intradermal injection of ACTH (50% Armour Standard) in a dilution of 1 1000 and a negative response to pork extract in a 1 500 dilution

4 D V age 23 gave an allergic history to many foods but not to pork ACTH was administered for 8 days in a daily dosage of 100 mgs for 2 days 60 mgs for 4 days 50 mgs for 2 days The product used was Armour Standard and the clinical response was good The full potency ACTH was replaced by 10 mgs of a 50% potency Armour ACTH administered 4 times a day The day following this change the patient complained of nervousness insomnia tachycardia weakness and pruritus at the site of injection Medication was continued The following day the pulse rate rose to 130 per minute the insomnia increased she became apprehensive and red indurated areas appeared at the site of injection Medication was discontinued

She was given skin tests with ACTH pork extract with a saline

control There was no reaction to any of the above as indicated by wheal, pseudopodia or erythema

The eosinophile count varied between 900 and 2200 when ACTH was not administered

Four cases out of 19 investigated with ACTH have given evidence of intolerance Because of this experience it is suggested that patients to be injected with ACTH be given small initial doses until their tolerance for the material is determined

DR CHARLES A L STEPHENS JR We have had opportunity to study 25 patients who have received ACTH during the course of our investigations in amino acid metabolism The majority of the cases studied suffered from rheumatoid arthritis With the exception of 2 cases with advanced destructive joint disease all who received the medication enjoyed dramatic remission in the activity of the rheumatoid arthritis but the return of symptoms following cessation of treatment was quite variable All patients were in a metabolic ward for a preliminary control period and throughout the treatment period

Of special interest were the following cases

Case 1 (Fig 18)

This patient (M W) is a 50 year old white female who had suffered from moderately severe peripheral rheumatoid arthritis for 5 years She was given 40 mg of ACTH daily in divided doses for a total period of 8 days and 20 mg per day in divided doses for 4 days following and then the medication was discontinued During the period of treatment the sedimentation rate fell rapidly to normal and subjective and objective signs of rheumatoid arthritis pain, stiffness and tenderness disappeared The eosinophils fell to low values and the total white blood count rose The patient felt the usual sense of well being followed by stimulation and mild insomnia This typical response of rheumatoid arthritis to ACTH therapy is of interest in this patient because she had undergone a splenectomy for hypersplenism some 3 years previously Thus it does not seem that an intact spleen is essential for either adrenal cortical stimulation by ACTH nor for the activation of the remission factor of rheumatoid arthritis *This* patient also is of interest because she had suffered for the previous 4 years from Sjogren s syndrome characterized by dryness of the mouth and the absence of tears in the eyes (keratoconjunctivitis sicca) This was so severe that obliteration of the tear duct had been recommended She required a lozenge in her mouth almost constantly Following the onset of ACTH therapy there was no effect on the Sjögren s syndrome until the tenth day of treatment at which time the patient awoke in the morning with increased saliva in the mouth

and she had the abilit to read for over one hour without ocular dis comfort The last day of treatment saliva and tears were plentiful and the patient appeared to have recovered from her long standing Sjogren's syndrome

Case 2 (Fig 19)

This patient was a 54 year old white female who had suffered from very severe rheumatoid arthritis for the previous 21 months

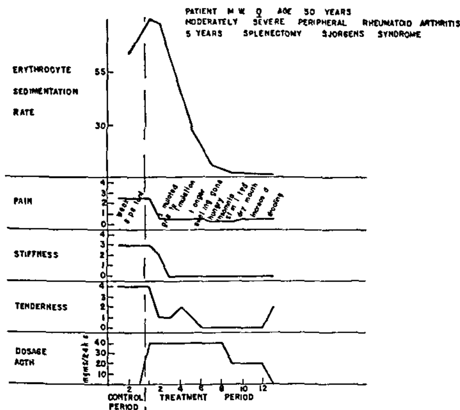


Fig 18

The patient was given 80 mg of ACTH per 24 hours for 8 days The rheumatoid arthritis responded in typical fashion and the laboratory values underwent the typical favorable alterations Of special interest however was the presence of bronchial asthma in a severe form which had required for over a year the continuous use of aminophylline by rectum and inhalations of epinephrin like substances at frequent intervals Within 24 hours after the beginning of ACTH therapy the patient's asthma disappeared During the entire course of treatment

and for some 3 months afterward there was no recurrence of the asthma After this period however, the asthma recurred

Case 3 (Fig 20)

This patient was a 33 year old white male, who had suffered from peripheral rheumatoid arthritis and rheumatoid spondylitis for the previous 7 years For 24 years the patient had suffered from unremitting generalized psoriasis An initial control period of 4 days was

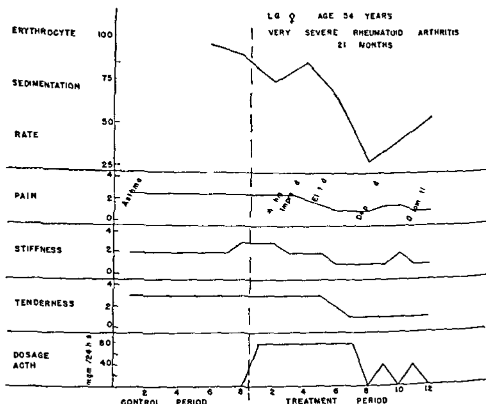


Fig 19

followed by 6 days of treatment with 100 mg of adenosine triphosphate (ATP) per 24 hours, in divided dosage There was no effect on the rheumatoid arthritis the rheumatoid spondylitis, nor the psoriasis However, on the seventh and subsequent days, the patient was given 40 mg of ACTH per 24 hours in divided dosage and within 4 days the psoriasis was completely gone No scale erythema nor pigmentation remained Concomitantly the symptoms of pain stiffness and tenderness disappeared Following cessation of treatment new psoriatic areas appeared within 48 hours and there was a rapid

exacerbation of the rheumatoid arthritis and spondylitis Attempts are now under way to reproduce this phenomenon in the same patient under identical conditions

Comment

It is of considerable note that ACTH was effective in one case of rheumatoid arthritis who did not have a spleen and who also enjoyed

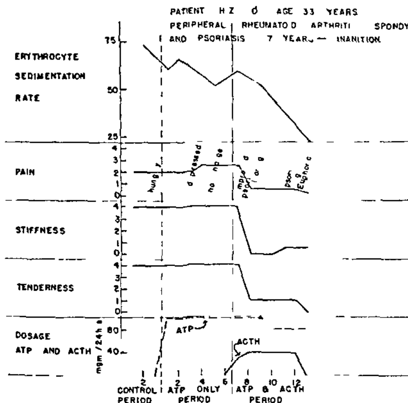


Fig 20

a remission of Sjogren s syndrome Also it is of interest that bronchial asthma disappeared during and for some time following the treatment and that psoriasis which had been present for 24 years cleared completely within a short space of time

Of greater interest however is the effect of small doses of ACTH (Armour's Standard) on rheumatoid arthritis and on the incidental or associated diseases mentioned In 14 patients with rheumatoid arthritis so far studied only 40 mgm of the medication was given in each 24 hour period Although the eosinophil counts were depressed

the total white counts rose the sedimentation rates fell to normal, and no alterations of blood pressure nor of quantitative urinary sugar determinations were noted Rapid and dramatic remission of the rheumatoid arthritis was a constant feature There was no alteration in daily body weights probably because the patients were on constant dietary intake The failure to exhibit weight changes on a constant diet suggests that there were no major alterations in sodium or fluid balance Complete remission in the absence of toxicity and with minimal metabolic changes, is of special speculative interest and suggests a dissociation between the remission factor and the known metabolic alterations associated with ACTH therapy

29

Metabolic Effects of Cortisone and ACTH in Cases of Rheumatoid Arthritis

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MAYO CLINIC ROCHESTER MINN

Following the demonstration of the profound effects of 17 hydroxy 11 dehydrocorticosterone (cortisone) and of adrenocorticotrophic hormone (ACTH) on the course of rheumatoid arthritis by Hench Kendall Slocumb and Polley [1] we undertook a study of the metabolic effects of these hormones in 5 patients with rheumatoid arthritis * Balance studies† for sodium potassium chloride nitrogen calcium and phosphorus were carried out and studies of the effects of the hormones on the plasma electrolytes were made For purposes of metabolic study cortisone or cortisone acetate was administered intramuscularly in doses of 100 or 200 mg daily and ACTH in doses of 100 or 105 mg daily The influence of simultaneous administration of estrone and of testosterone propionate on the metabolic effects of cortisone acetate was studied in 1 patient The effects of 900 mg of 17 hydroxycorticosterone (compound F) administered in a period of 12 days were studied in 1 patient ‡

In each instance the clinical response of the arthritis was as previously described by Hench Kendall Slocumb and Polley [1] As might have been expected the extent of the metabolic effects which were

* The collaboration of Drs P S Hench C H Slocumb and H F Polley in these studies is acknowledged

† The authors are indebted to Miss Gordon Sampson chief dietitian Mayo Clinic metabolic unit St Marys Hospital for her careful planning and preparation of the diets used in metabolic balance studies

‡ The authors are indebted to Merck & Co Inc and to Dr James M Carlisle Medical Director for the supplies of cortisone and cortisone acetate used in this study to Armour and Company and to Dr John R Mote Director of Medical Research for the supplies of ACTH to the Upjohn Company and to Dr E Gifford Upjohn for the supply of 17 hydroxycorticosterone (compound F)

observed was directly related to the dose of cortisone employed However the observed metabolic effects of the hormones and the clinical response of the arthritis apparently were not related

OBSERVATIONS*

Case 1

The patient a man 34 years of age had had rheumatoid arthritis for 4½ months He received 100 mg of free cortisone daily for 5 periods of 6 days each The alterations in the concentrations of the plasma electrolytes induced by cortisone in this case are shown in Fig 1 and corresponding balance data are shown in Fig 2 Only slight changes in the plasma electrolytes were observed, mild alkalosis developed during administration of cortisone The concentration of plasma potassium did not decrease significantly

The balances for sodium and chloride were positive during the control period (periods 1 to 3, Fig 2) The excretion of sodium and chloride increased gradually during the first 3 periods of administration of the hormone (periods 4, 5 and 6) so that in the third period (that is period 6) the balances became negative During the next two periods of administration (periods 7 and 8) the balances for sodium and chloride again became positive Excretion of nitrogen also increased slightly during administration of cortisone (Fig 3) the balance becoming negative in the fourth and fifth periods of administration of the hormone (that is, in periods 7 and 8) The changes in the urinary excretion of calcium and phosphorus did not appear to be significant but the quantity of calcium and phosphorus excreted in the feces seems to have been increased by cortisone

The metabolic effects of cortisone in a dose of 100 mg daily for the 30 days during which these effects were studied were not pronounced in this case

Case 2

The metabolic effects of 100 mg of cortisone daily for 12 days in a man 40 years of age who had had chronic rheumatoid arthritis for 2 years were studied No significant changes in the concentrations of the plasma electrolytes and in the balances of nitrogen potassium calcium and phosphorus occurred Retention of sodium and chloride, however increased slightly in the second 6 days of administration of the hormone

Although the metabolic effects of cortisone in a dose of 100 mg daily in cases 1 and 2 were not pronounced, as far as they were

* Cases 1 2 3 4 and 5 are cases 5 4 14 11 and 6 respectively of the papers by Hench Kendall Slocumb and Polley[1] and Sprague Power Mason and others[2]

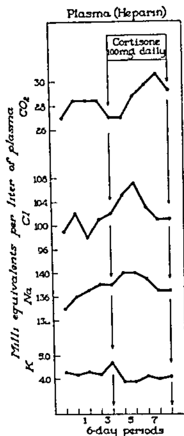


FIG 1 Case 1 Minimal alteration of plasma electrolytes during administration of 100 mg of cortisone daily Mild alkalosis developed From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* **85** 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

measured the clinical effects of cortisone on the rheumatoid arthritis in the 2 cases as described by Hench Kendall Slocumb and Polley [1] were dramatic

Case 3

This patient a woman 45 years of age had moderately severe chronic rheumatoid arthritis for 5 years Roentgen therapy of the ovaries had induced artificial menopause 4 years before registration at the Mayo Clinic

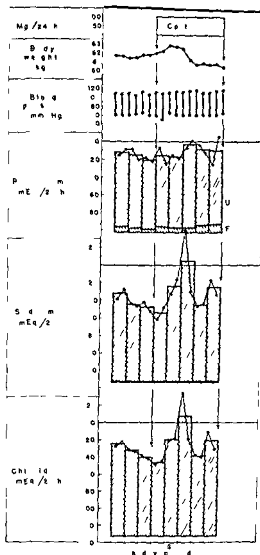


FIG 2 Case 1 Body weight blood pressure and balance data for potassium sodium and chloride From Sprague R G, Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb, C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

More pronounced changes occurred in the plasma electrolytes and pH of the blood during and following administration of several hormones in this case than in any of the other cases studied The patient received ACTH cortisone acetate, cortisone acetate plus estrone and cortisone acetate plus testosterone propionate for varying periods and the alterations were noted (Figs 4 and 5)

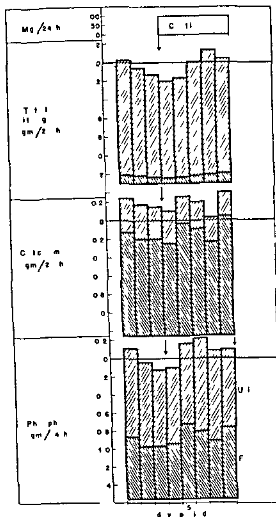


FIG 3 Case 1 Balance data for nitrogen calcium and phosphorus From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

The values for plasma electrolytes were determined at intervals of 6 days In the 12 days during which 100 mg of ACTH was administered daily the concentration of plasma bicarbonate increased those of potassium and sodium decreased and that of chloride decreased markedly The most marked changes were observed at the end of the period of administration of ACTH Six days after doses of

ACTH were stopped, the concentrations of plasma electrolytes had re turned to normal On the first 2 days of administration of ACTH, marked retention of sodium and chloride and slight loss of potassium were noted (Fig 5) Subsequently, the excretion of sodium, potas sium and chloride increased above the control levels so that the net balances of the last two ions were markedly negative during the 12

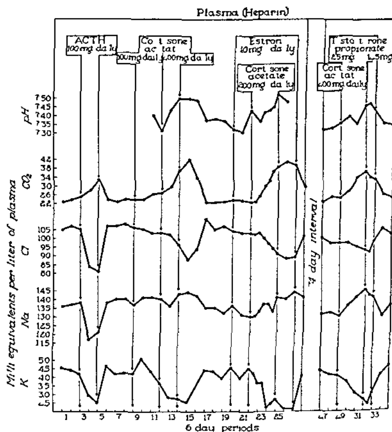


FIG 4 Case 3 Alterations in plasma electrolytes induced by ACTH and cortisone acetate From Sprague R G Power M H Albert A Mathie son D R Hench, P S Kendall E C Slocumb C H and Polley, H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

days of administration of ACTH With cessation of administration of ACTH, marked retention of chloride and potassium and slight re tention of sodium compensated for the previous loss of these elec trolytes (see Fig 5)

Cortisone acetate was administered subsequently in a dose of 100 mg daily for 18 days, immediately thereafter 200 mg was given

daily for 12 days The values for plasma electrolytes changed only slightly during 18 days when the dose was 100 mg daily (see Fig 4) A rather severe hypochloremic hypokaliemic alkalosis occurred during and after the administration of the hormone in a dose of 200 mg daily It was similar in all respects to the alkalosis which is observed

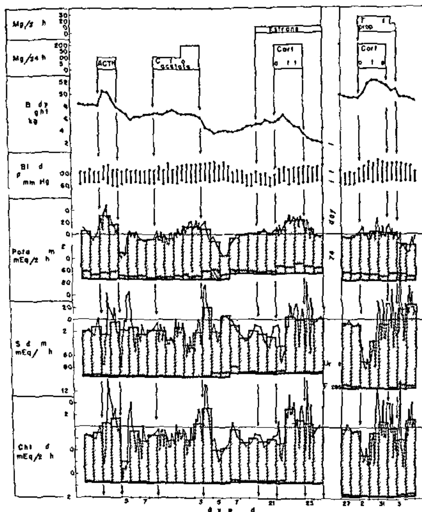


Fig 5 Case 3 Body weight blood pressure and balance data for potassium sodium and chloride From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* **85** 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

in some cases of Cushing's syndrome The most marked changes were observed 12 days after administration of the hormone was stopped Subsequently, the values gradually reverted to normal The highest pH of blood observed was 7 50 In contrast to the decrease in plasma sodium during administration of ACTH there was a slight increase in plasma sodium after administration of cortisone acetate As a result of this the rise in plasma bicarbonate was more marked immediately after administration of cortisone acetate was stopped than had previously been observed during administration of ACTH During or at the end of the 30 days of administration of cortisone acetate, balances for potassium, chloride and sodium became negative (Fig 5) The loss of sodium did not become apparent until the first 6 day period after stopping administration of the hormone The excretion of chloride, on the other hand, increased slightly beyond the intake in the last period of administration of cortisone acetate (that is period 13) and the chloride balance became more markedly negative in the first period after cessation of administration of the hormone (that is, period 14) On the basis of other observations concerning the duration of effect of cortisone acetate after administration was stopped the loss of sodium and chloride in period 14 was probably due to a continuing hormonal effect rather than to withdrawal of the hormone The retention of sodium and chloride which occurred in period 15 when the physiologic effect of the hormone was presumably waning substantiates this opinion

The simultaneous and previous administration of estrone in a dose *of 10 mg daily did not modify significantly the effects of 200 mg daily* of cortisone acetate on the concentrations of the plasma electrolytes and on electrolyte balances (see Figs 4 and 5)

The simultaneous administration of cortisone acetate in a dose of 200 *mg daily and testosterone propionate in* a dose of 25 mg daily did not induce the loss of nitrogen which was previously observed during administration of cortisone acetate alone (see next paragraph) and the loss of potassium was less than had previously been observed with cortisone acetate alone Nevertheless the development of hypochloremic, hypokaliemic alkalosis under the influence of cortisone acetate was not prevented by testosterone in this dosage (Fig 4)

A negative nitrogen balance of considerable magnitude was observed during administration of ACTH cortisone acetate and cortisone acetate plus estrone (Fig 6) As mentioned previously, an increase in excretion of nitrogen was prevented by the simultaneous administration of testosterone propionate Changes in urinary excretion of calcium and phosphorus were generally slight or absent during administration of cortisone acetate Significant increases in urinary excretion of calcium and phosphorus occurred during administration of

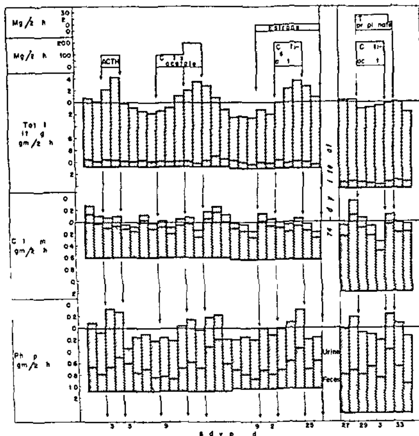


Fig 6 Case 3 Balance data for nitrogen calcium and phosphorus From Spra ue R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199 258 (Feb) 1950 Courtesy of the publisher American Medical Association

ACTH During and after all 4 programs of treatment excretion of phosphorus in feces was significantly increased

Case 4

For 5 years the patient a woman 40 years of age had had moderately severe chronic rheumatoid arthritis The behavior of the plasma electrolytes and balance data for electrolytes during administration of ACTH in a dose of 105 mg daily for 12 days and cortisone acetate in a dose of 200 mg daily for 18 days are shown in Figs 7 and 8 In general changes observed were similar to but of somewhat smaller magnitude than those observed in case 3 During

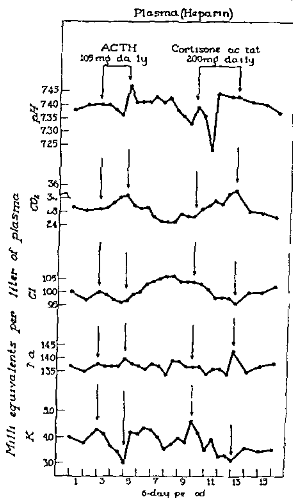


FIG 7 Case 4 Alterations in plasma electrolytes induced by ACTH and cortisone acetate From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199-258 (Feb) 1950 Courtesy of the publisher, American Medical Association

and after administration of ACTH and subsequently during and after administration of cortisone acetate hypochloremic hypokaliemic alkalosis developed Sodium and chloride were retained during the first two periods of administration of cortisone acetate but in the third period of administration and in the first period following withdrawal the balances became negative In the second period of administration of ACTH and in the third period of administration of cortisone acetate the balance for potassium became negative

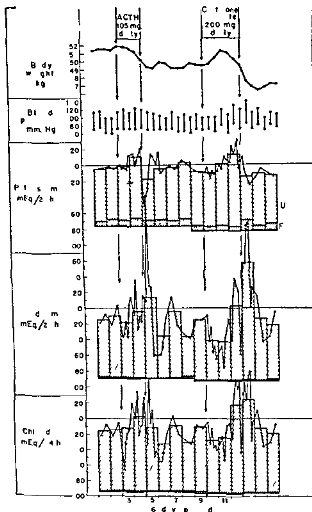


FIG 8 Case 4 Body weight blood pressure and balance data for potassium sodium and chloride From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

A negative nitrogen balance of considerable magnitude developed in the course of administration of both ACTH and cortisone (Fig 9) There was a small but probably significant increase in urinary excretion of calcium and phosphorus during administration of cortisone Excretion of calcium and phosphorus in feces varied widely in the

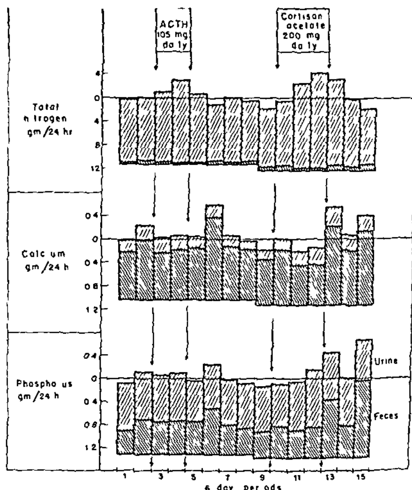


Fig 9 Case 4 Balance data for nitrogen calcium and phosphorus From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H, and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

period covered by the study In period 13 after administration of cortisone was stopped it was rather markedly increased

Case 5

The patient a woman 49 years of age had suffered from severe chronic rheumatoid arthritis for 3 years The changes in the concentration of the plasma electrolytes and in the balance for electrolytes produced by ACTH 17 hydroxycorticosterone (compound F) and cortisone acetate are shown in Figs 10 and 11 The alterations in the

concentrations of the plasma electrolytes during and following administration of ACTH in a dose of 100 mg daily were qualitatively similar to those previously observed in cases 3 and 4 The concentrations of potassium sodium and chlorides all decreased The decrease

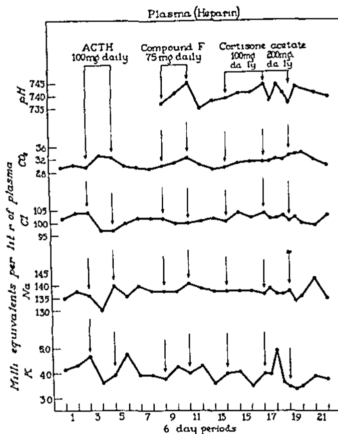


FIG 10 Case 5 Changes in plasma electrolytes induced by ACTH Compound F and cortisone acetate From Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

in plasma chlorides was of greater degree than the decrease of sodium and gave rise to a moderate increase in bicarbonate The hypochloremic hypokaliemic alkalosis resembled that which is seen in some cases of Cushing s syndrome except that the concentration of plasma sodium was reduced The balance data indicate that initially there was a marked retention of sodium and chloride but that in the

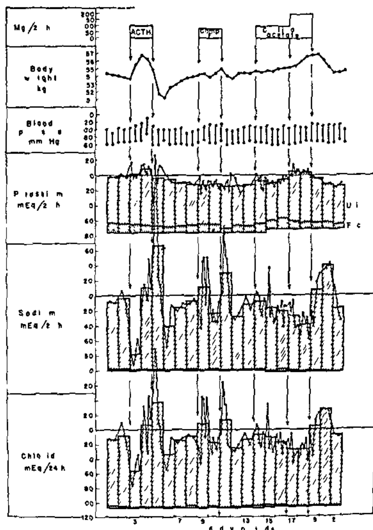


Fig 11 Case 5 Body weight blood pressure and balances of potassium sodium and chloride From Sprague R G Power M H Mason, H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medical Association

second period of administration of ACTH (period 4), the balances for these ions became negative When administration of ACTH was stopped there was a marked loss of chloride and an even more marked loss of sodium (period 5) In period 6 however, sodium and chloride were retained During the two periods of administration of ACTH

moderate loss of potassium occurred and in succeeding periods potassium was retained

An average daily dose of 75 mg of compound F for 12 days to this patient resulted in mild alkalosis There was however no significant change in the level of plasma sodium or potassium The balances of sodium and potassium varied during and after administration of compound F In period 9 the first period of administration the balances for both sodium and chloride were slightly negative but in the second period of its administration these balances became positive In the first period after use of compound F was stopped (period 11) there was a rebound with a loss of chloride and a more marked loss of sodium Sodium and chloride were retained in decreasing degree in the two succeeding periods (periods 12 and 13)

When a dose of 100 mg of cortisone acetate daily was given for 18 days and this was followed by daily doses of 200 mg for 12 days alkalosis which was qualitatively similar to that previously observed in cases 3 and 4 developed Balance studies indicated retention of sodium and chloride during administration of the hormone However in the two metabolic periods after administration of the hormone was stopped (that is periods 19 and 20) the balances for these ions became negative Whether the loss of sodium and chloride under these conditions was due to continuing action of cortisone acetate after cessation of its administration or to withdrawal of the hormone is problematic However other studies in which the balances for sodium and chloride became negative during administration of cortisone acetate suggest that it may be due to the former

Nitrogen balance became negative during administration of ACTH and cortisone acetate but not during administration of compound F (Fig 12) Urinary excretion of calcium and phosphorus increased during administration of ACTH and cortisone In the two periods following the administration of ACTH (periods 5 and 6) the calcium excreted in feces decreased greatly An increase in excretion of phosphorus in feces seems to have followed administration of ACTH and cortisone acetate especially the latter

Changes observed in plasma calcium during the course of metabolic balance studies in these 5 cases were not significant During or soon after periods of administration of ACTH or cortisone the plasma inorganic phosphorus decreased slightly

SUMMARY

In 5 cases of rheumatoid arthritis a study was made of some of the metabolic changes induced by the administration of ACTH corti one

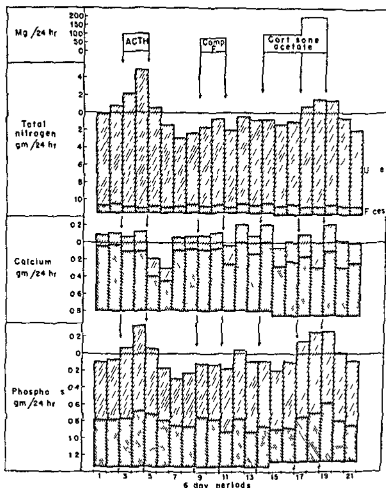


FIG 12 Case 5 Balances of nitrogen calcium and phosphorus From Sprague R G Power M H Mason, H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H , and Polley H F Observa tions on the physiologic effects of cortisone and ACTH in man *Arch Int Med* 85 199–258 (Feb) 1950 Courtesy of the publisher American Medi cal Association

and cortisone acetate In 1 of these cases the effects of compound F were studied also

A negative balance for nitrogen and potassium followed the ad ministr ition of ACTH in a daily dose of 100 mg for 12 days to 2 pa tients (cases 3 and 5) and 105 mg daily for 12 days to 1 patient (case 4) During administr ition of this hormone there was initially a marked retention of sodium and chloride and then increased ex cretion of these ions Hypochloremic hypokalemic alkalosis ac

companied by some lowering of the serum sodium developed in each case

When cortisone was administered in a dose of 100 mg daily for 12 to 30 days the balances for nitrogen calcium phosphorus sodium potassium and chloride and the concentrations of the plasma electrolytes (cases 1 and 2) altered only slightly or not at all Mild lowering of the plasma potassium was occasionally encountered

When cortisone acetate was given in a dose of 200 mg daily for 12 to 18 days the balances for nitrogen and potassium regularly became negative The effects on excretion of sodium and chloride were variable the most common was retention of these ions early in the period of administration of the hormone followed later by increased excretion At this dose level hypochloremic hypokaliemic alkalosis developed it was similar in all respects to that observed in some cases of Cushing s syndrome After withdrawal of the hormone the pattern of the blood electrolytes gradually became normal

The prior and simultaneous administration of 10 mg of estrone daily did not modify the metabolic changes induced by cortisone acetate in a woman in whom artificial menopause had been induced 4 years previously (case 3) The simultaneous administration of 25 mg of testosterone propionate daily with the cortisone acetate in this case however obviated an increase in excretion of nitrogen and minimized loss of potassium but failed to prevent hypochloremic hypokaliemic alkalosis

Compound F in total dose of 900 mg in 12 days did not induce any pronounced metabolic changes A slight decrease in plasma chlorides and alkalosis of mild degree were noted

These studies did not show any correlation between the metabolic changes which resulted from the administration of ACTH cortisone and compound F and the favorable clinical effects of these hormones on the rheumatoid arthritis of these patients

REFERENCES

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2 Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F Observations on the physiologic effects of cortisone

and ACTH in man, *Arch Int Med*, 85 199–258 (Feb) 1950 Courtesy of the publisher, American Medical Association

DISCUSSION

DR MARIAN W ROPES This patient (M M) received, as you will remember, 150 mgm of cortisone daily 30 mgm of desoxycorticosterone glucoside, a combination of these two, and 100 mgm of ACTH (Fig 13)

It will be noted that the effect on potassium was immediate in all treatment periods—a slightly increased output with cortisone a very slight increase with desoxycorticosterone more with desoxycorticosterone and cortisone than the summation of those with desoxycorticosterone and cortisone and even greater with ACTH There was retention after each treatment period

The urinary calcium was increased with cortisone therapy We have not finished the stool and urine studies It looks as though there was a greater increase in urinary calcium with cortisone plus desoxycorticosterone

The serum phosphorus fell during each period of treatment except the desoxycorticosterone The phosphorus excretion was very much like that found by Dr Sprague There was a slight increase in fecal phosphorus on cortisone and desoxycorticosterone and cortisone The fecal output was increased on ACTH Nitrogen excretion showed relatively little change a slight retention on desoxycorticosterone and a slight loss on ACTH The creatine excretion was decreased on cortisone, and at the end of the desoxycorticosterone period, and stayed down during treatment with desoxycorticosterone and cortisone and went down at the end of ACTH

Fig 14 shows the sodium and chloride changes Sodium retention took place immediately with cortisone therapy though the total retention during treatment was not great With cessation of therapy, the output increased markedly but was followed by a big rebound With desoxycorticosterone therapy there was more retention but less rebound post therapy On desoxycorticosterone plus cortisone there was definite retention and an output after treatment which seems as much as, if not more than the added effect of cortisone and desoxycorticosterone

I think this is of extreme interest in view of the so called paradoxical effects shown yesterday by Dr Forsham in which apparently it seemed that desoxycorticosterone counteracted the effect of cortisone In our results they add together if not increase each other s effect The results on ACTH were what one would expect

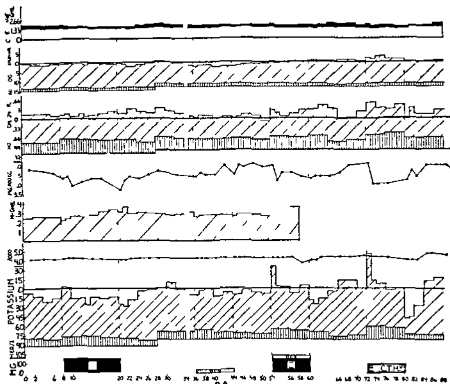


FIG 13

DR F L ENGEL In one case of Cushing s disease with adrenal cortical carcinoma with hypokaliemia and alkalosis we were able to overcome the alkalosis with 100 mgs of testosterone propionate daily I wonder whether Dr Sprague might find this same effect with larger doses of testosterone propionate in arthritis treated with compound E?

DR PETER H FORSHAM I would like to comment on Dr Ropes last statement about the paradoxical sodium effect of cortisone and DCA

We didn t mean to imply that DCA counteracted the sodium retaining effect of cortisone On the contrary cortisone we believe counteracts some of this effect of DCA when the latter is given in large amounts from 4 to 5 mgs a day

In terms of desoxycorticosterone giving 30 mgs of desoxyglucoside is extremely little because only half of that molecule is active desoxycorticosterone and a lot of the glucoside is excreted immediately in the urine thus the patient received not more than about 10 mgs of desoxycorticosterone a day maybe less That is a very small dose in the normal The results therefore in no way invalidate the

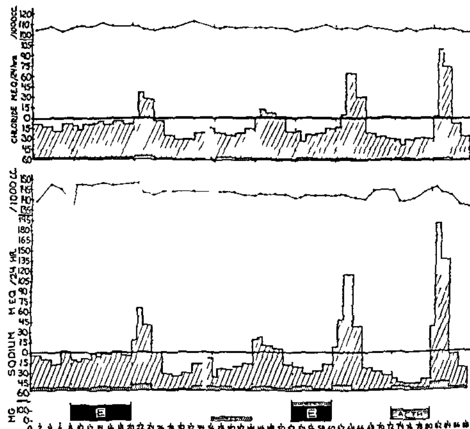


Fig 14

findings of Selye which have since been repeated in rats by Swiss workers

Finally as regards the hypochloremic alkalosis we found the same type of low potassium alkalosis in our induced Cushing s syndrome and we were able to correct that within 3 days by giving 3 gms of K Cl a day p o This was merely repeating an experiment which had been reported by the late Dr Kepler

DR WALTER BAUER I don t think we have a right to conclude that Selye produced an endocrine arthritis The arthritis is polyarticular in nature and of the acute inflammatory destructive type Until the involved joints have been cultured for *Streptobacillus moniliformis* and L organisms, both common in rats and reported to be negative we should not continue to refer to this type of joint disease as an endocrine arthritis

DR LAURANCE W KINSELL I would like to comment on one finding in Dr Sprague s charts namely increase in fecal calcium and phosphorus excretion during the administration of ACTH

We were most relieved to hear one investigator report similar findings yesterday We found the same thing and were concerned that it might be a laboratory error We wonder since this is apparently a valid observation whether anyone has any data which would indicate whether this refers to some inhibition of absorption of calcium and phosphorus in the gut or whether it relates to actual increased biological excretion into the gut

We think the latter is the more probable In one part of our data there was actually a greater amount of calcium in the stool than could be accounted for on the basis of intake

DR ROGER A LEWIS I think a little attention should be paid to the general effect of large doses of ACTH and Cortisone on the gastro intestinal tract We found several years ago that the fat content of the stool decreased markedly and our experimental animals seemed to be constipated when large quantities of compound E were given The reduction in fat content and the constipating effect of E and ACTH might explain some of the changes in calcium excretion that have been reported here and might also throw some light on the effect of ACTH on ulcerative colitis which has also been mentioned

DR C H SLOCUMB (Mayo Clinic Rochester Minn) I wish when cases are reported they would report as to whether or not the patients are men or women and also regarding the women s menstrual cycle I want to emphasize in the first case the patient had a profound change in the electrolyte pattern This patient was a menopausal patient Her ovaries had been treated 10 years ago by x ray

The next two patients whose menstrual cycles were quite intact had distinctly less electrolyte changes than the first patient We seemed to run into difficulty both in the electrolyte balance and fullness of the face and increased growth of hair when they had some alteration in their menstrual cycle I can t help but feel that the maintenance of a normal menstrual cycle is associated with a minimum of hirsutism although it may not preclude an appreciable electrolyte change taking place

It is apparent that estrone had no effect on the electrolyte pattern I am not sure if it has an effect on the hirsutism As a clinician I want to point out that the electrolyte changes are very interesting they are very necessary we must have them for protection against some phases of toxicity and for understanding of the mechanism of action but as a

clinician you can t get away from the very profound effect that ACTH has on fibrous tissue, lymphoid tissue, and muscle, both clinically and microscopically, and the electrolyte studies have not aided in the understanding of mechanism of action of ACTH in these tissues

DR WALTER BAUER I think the age and sex of some of these patients has been indicated on the charts Dr Slocumb

DR JAMES J SMITH The reaction by sex has impressed us greatly I have found in general in a preliminary way, that acute alcoholic women who respond to adrenocortical extract favorably, if they are in their active reproductive life do not seem to respond to ACTH, whereas post menopausal women do One acutely alcoholic woman for example to whom we gave ACTH had just started a menstrual period, and ACTH didn t do anything for her whereas ACTH given to a post menopausal acutely alcoholic woman with mild pellagra cleared this patient up very quickly

DR RANDALL G SPRAGUE I am sure Dr Forsham didn t mean to imply that potassium chloride is the treatment for Cushing s syndrome It has been known for a long time that potassium chloride will correct the blood electrolyte abnormality of Cushing s but not the other manifestations of the syndrome As a corollary to this it is apparent that potassium chloride is not the answer to all the undesirable effects which may result from prolonged administration of ACTH or cortisone

I was glad to hear Dr Kinsell s comments on the changes in fecal calcium and phosphorus We have no information about mechanism but, like Dr Kinsell I would be inclined to favor an increased excretion of calcium and phosphorus into the gastrointestinal tract rather than a diminished absorption However we have no evidence to prove this

There is one other sidelight which there was not time to mention namely, the occurrence of pigmentation in patients who receive ACTH We have observed it in one patient who was a swarthy complexioned individual The pigmentation closely resembled that seen in Addison s disease The ACTH preparation was found by Dr Albert to contain appreciable amounts of melanophore hormone (intermedin) on bioassay in hypophysectomized frogs

DR CHARLES RAGAN Our group working in the field of rheumatic diseases has been inclined to agree with Dr Slocumb that the changes in electrolytes keto steroid and oxy steroid excretion etc , described at this meeting may have little bearing on the clinical remission in

patients with rheumatic diseases treated with ACTH We would like to report on some preliminary observations we have made Two patients with lupus erythematosus disseminatus developed open wounds while on ACTH therapy, one a decubitus ulcer, the second an incised and drained parotid abscess In both of these wounds no granulation tissue appeared while on ACTH When ACTH was discontinued in one patient granulation tissue appeared in the wound in 4 days following withdrawal of the hormone Two patients have had clean biopsy wounds which healed very slowly while on ACTH In both a second biopsy healed promptly when ACTH was discontinued Working with Dr Howes of the Department of Surgery cortisone given to rabbits in large doses has inhibited the development of granulation tissue From these preliminary observations it may be suggested that these materials ACTH and cortisone depress the activity of the connective tissue The symptomatic remission of these diseases many of which have been called connective tissue diseases may at least in part be related to this depression of activity of the connective tissue

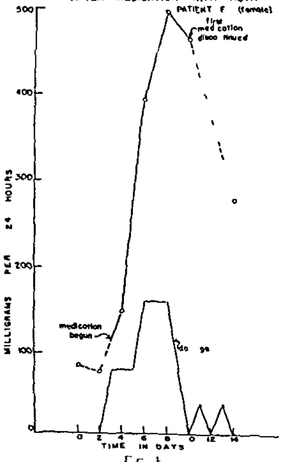

APPARENT FREE HISTIDINE EXCRETION
AFTER MEDICATION WITH ACTH
PATIENT K (male)
MILLIGRAMS PER 24 HOURS
400
300
200
100
0
medication begun
first medication discontinued
dosage
0
2
4
6
8
10
12
14
TIME IN DAYS

Fig 3

APPARENT FREE HISTIDINE EXCRETION
AFTER MEDICATION WITH ACTH
PATIENT F (female)
first medication discontinued
MILLIGRAMS PER 24 HOURS
500
400
300
200
100
0
medication begun
TIME IN DAYS

Fig 4

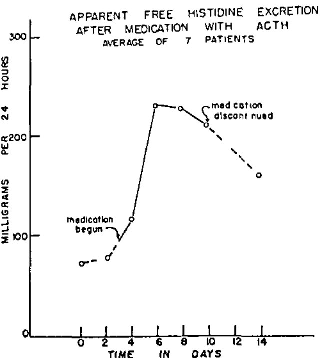

APPARENT FREE HISTIDINE EXCRETION
AFTER MEDICATION WITH ACTH
AVERAGE OF 7 PATIENTS
MILLIGRAMS PER 24 HOURS
300
200
100
0
medication begun
med cation discont nued
0 2 4 6 8 10 12 14
TIME IN DAYS

Fig 5

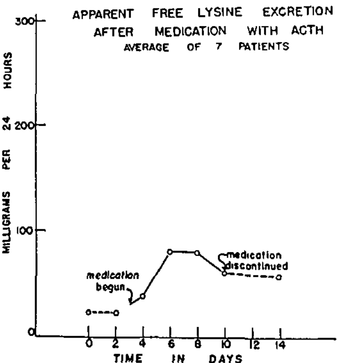

APPARENT FREE LYSINE EXCRETION
AFTER MEDICATION WITH ACTH
AVERAGE OF 7 PATIENTS
MILLIGRAMS PER 24 HOURS
300
200
100
0
medication begun
medication discontinued
0 2 4 6 8 10 12 14
TIME IN DAYS

Fig 6

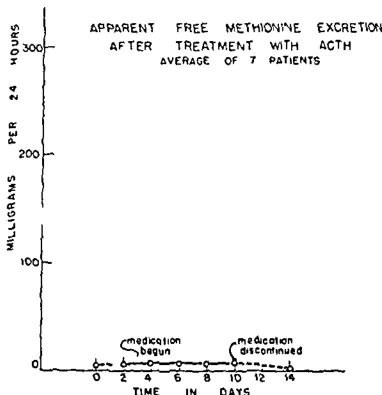


Fig 7

	CONTROL	INCREASE ABOVE CONTROL	INCREASE AT PEAK
	← milligrams	per 24	hours →
HISTIDINE	74 7	118 4	195 7
LYSINE	21 8	41 8	72.1
METHIONINE	5 4	1 0	2.3

Fig 8 Average increase in apparent amino acid excretion during medication with ACTH Average of 7 patients

cretion The figures (not on the chart) for Cortisone remission are comparable with those for ACTH

(Figs 2, 3 and 4) These show typical individual curves for histidine excretion on ACTH medication Subsequent experience using

only 40 mg of ACTH daily on 11 patients, gave similar histidine (and other amino acid) curves associated with remission of disease

(Fig 5) This indicates the average curve of 7 active rheumatoid arthritis patients on metabolic control before and during administra-

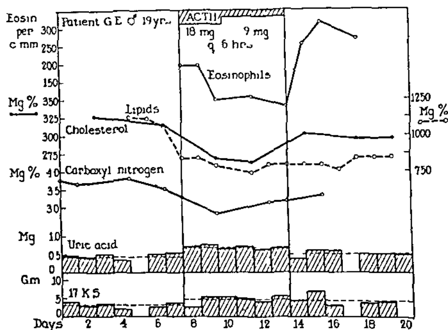


Fig 9

tion of ACTH (histidine excretion is markedly increased during ACTH remission)

(Fig 6) The same 7 patients as shown in Fig 5 indicating the increase in lycine excretion

(Fig 7) Methionine excretion is shown in the same 7 patients and while very slight increased excretion occurred the curve is relatively flat

(Fig 8) This table shows the comparison between histidine lycine and methionine At the peak histidine excretion is increased over 250% and lycine over 300% during ACTH remission

From these preliminary observations no conclusions can be drawn It is possible that these amino acid patterns are constantly associated with remission To determine this we are now attempting to produce such patterns without remission and to produce remission without such amino acid patterns Further studies should clarify the role (if

any) of amino acid metabolism in the remission factor of rheumatoid arthritis

We have reported here some new observations regarding the changes in amino acid metabolism occurring with the administration of ACTH and Cortisone Additional studies may reveal whether these changes are actually dependent upon adrenocortical stimulation or whether the effective mechanism is quite different such as the alteration of an enzyme chain and possibly independent of such stimulation

DISCUSSION

DR R L GREIF (Rockefeller Institute New York City) We have measured the total plasma amino acid levels in a 19 year old patient with hypopituitarism and the results can be seen on the accompanying slide under the heading 'Carboxyl nitrogen It will be seen that *there has been a significant fall in the plasma amino acid level during* the administration of ACTH (Fig 9) These results are quite different from those of Li following administration of his preparation to rats We have not measured the total urinary excretion of amino acids

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The Effect of ACTH on Juvenile Rheumatoid Arthritis or Still's Disease

J Sydney Stillman and Theodore B Bayles

ROBERT BRECK BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

*It was the object of this study to determine the effect of ad*ministrations of ACTH to 3 children suffering from juvenile rheumatoid arthritis

It was originally planned to give each patient 3 courses of treatment with rest periods of 10 days between them Each course was to consist of 5 mg of ACTH every 6 hours for 10 days then 2 5 mg 4 times daily for 4 days This plan was followed in one patient but had to be modified in one because the first dose of the second course caused a severe hypersensitivity reaction Therefore after successful desensitization he received 20 mg daily for one month The third patient responded very well to the first two courses but did not to the third so that after 8 days the dose was increased to 8 mg every 6 hours with slightly increased effect Since immediately following the completion of this course she had a severe exacerbation she was given 40 mg daily for 20 days and then 20 mg for 2 days

Because of the different treatment schedules composite charts could not be made Therefore a summary of the effects will be presented and then the individual charts shown

The musculoskeletal symptoms promptly respond to treatment Stiffness and pain disappear in large measure during the first 24 to 48 hours The speed with which the range of motion of the joints can be traversed is particularly striking The increased warmth of the joint subsides almost as quickly as the pain The swelling particularly if marked is slower to disappear but with adequate dosage does subside within a week or 10 days Although the muscular weakness due to the inhibition caused by pain is quickly eliminated it takes weeks or months of exercise to rebuild severely atrophied muscles

The rapid pulse rate and elevated temperature fall within 3 or 4 days to normal levels Within 24 hours there is a feeling of well being and happiness With further treatment the patients display a buoyant

restlessness which is more than one would expect in healthy children One 4 year old boy developed the aggressive, overactive and objectionably spoiled behavior Selye has described in virilizing tumors of the adrenal cortex After treatment was stopped their moods and actions returned to normal The appetite and food intake increased enormously from their pre treatment anorexia There is an initial rapid gain in weight in the first 4 or 5 days with a subsequent partial drop which other studies of blood volume and sodium excretion lead us to believe are due to transient sodium and water retention There after a true weight gain occurred

Laboratory studies showed similar improvement The markedly elevated corrected sedimentation indices fell to normal in 10 days or less There was a rise in hematocrit of 10 to 15 points with corresponding increases in hemoglobin values and red cell counts During a course of treatment there is a rise of reticulocytes to 5 to 7% Marrow studies in adults show a marked erythropoiesis A complete study of the blood changes is the subject of a separate investigation There is a rise in initially high white blood counts up to as high as 48,000 The differential counts show the polys to average 85% almost all of which are mature many segmented forms Lymphocytes are markedly decreased but mononuclears show an absolute increase The eosinophiles drop sharply in 4 hours and remain at levels from 0–15 per cu mm during treatment After the completion of each of the early periods of treatment they rose promptly but at the completion of therapy after an initial rise they remained lower than the pre treatment levels In only one patient in two observations did the fasting blood sugar exceed the normal values and those only slightly The rises in 17 ketosteroids were satisfactory and in keeping with the age of the patients The hyperglobulinemia all patients showed before treatment was corrected In the one patient suffering from secondary amyloidosis there is as yet no indication that the process has been altered

The first patient is a boy, age 4 years who had the onset of his disease in October 1947 5 months before transfer to the hospital He was severely ill with generalized joint involvement except for a fairly good remission for several months at the beginning of this year

In Fig 1 sodium and water retention is evidenced in the weight graph at the beginning and end of each treatment period followed in every case by weight loss as diuresis of salt and water occurred

Fluctuations of pulse due to increased physical activity after initial clinical improvement

Prompt disappearance of joint symptoms and signs notable

Patient still in remission 5 weeks after treatment stopped

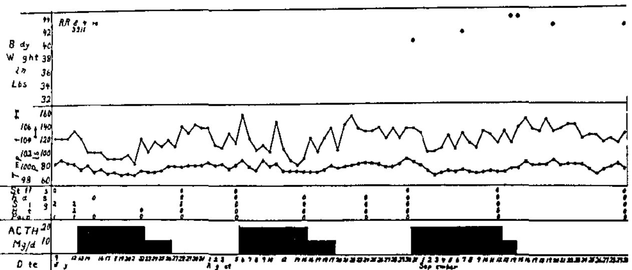


Fig 1

Fig 2

In Fig 2 note the sedimentation index drop during treatment the rise immediately following cessation, and then spontaneous drop

Rapid rise of hematocrit with treatment and partial fall on cessation

Eosinophile count decrease during treatment, rise immediately following end of treatment and then spontaneous recovery

Note reticulocyte response during second course of therapy

The second patient is a 6 year old boy who had the explosive onset of his disease in July 1948, 4½ months before transfer to the hospital He remained severely ill with generalized joint involvement, lymphadenopathy, high fever and all the laboratory evidence of marked activity until the time of treatment

In Fig 3 note the weight gain and maintenance after therapy

Temperature and pulse quickly fall to normal range with treatment and start to rise as soon as dosage is decreased

In Fig 4 the escape from ACTH effect with lower dosage is evi

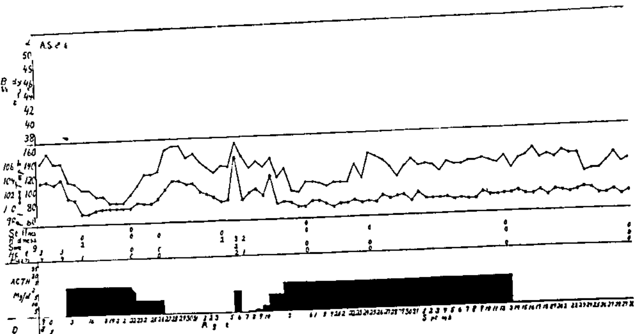


Fig 3

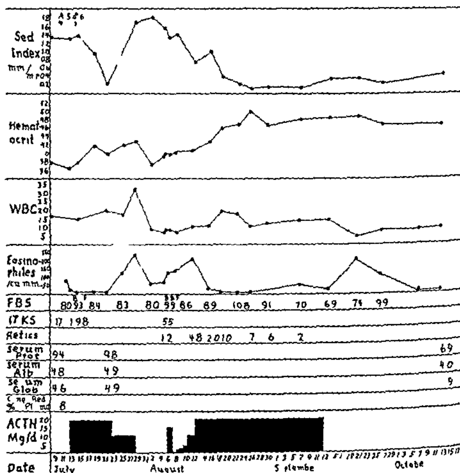


Fig 4

denced by the rise in sedimentation index, white blood count and eosinophiles

Hematocrits and reticulocytes

Patient still in remission 5 weeks after treatment stopped

In Fig 5 is shown the clinical response to 20 mg/d in a 14 year old girl of almost adult size

Fig 6 shows the failure to respond to the same dose in the third course

Partial response to 32 mg/d but immediate severe relapse

Excellent reaction to 40 mg/d

Fig 7 shows the failure of the sedimentation index to fall in the third course

Fasting blood sugars show rise to 125 mg % at end of prolonged large dosage of fourth course This is only abnormal fasting blood sugar in the three patients treated

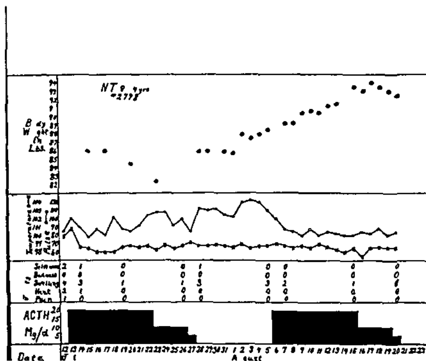


Fig 5

Fig 6

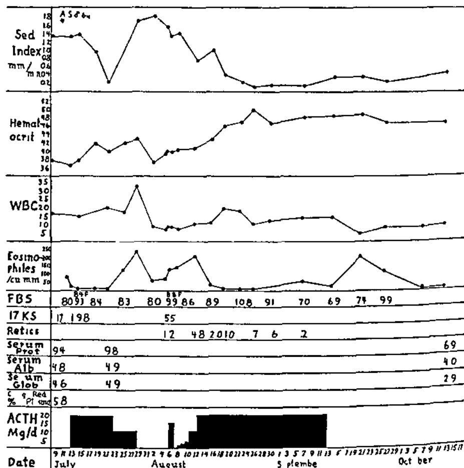


FIG 4

denced by the rise in sedimentation index white blood count and eosinophiles

Hematocrits and reticulocytes

Patient still in remission 5 weeks after treatment stopped

In Fig 5 is shown the clinical response to 20 mg/d in a 14 year old girl of almost adult size

Fig 6 shows the failure to respond to the same dose in the third course

Partial response to 32 mg/d but immediate severe relapse

Excellent reaction to 40 mg/d

Fig 7 shows the failure of the sedimentation index to fall in the third course

Fasting blood sugars show rise to 125 mg % at end of prolonged large dosage of fourth course This is only abnormal fasting blood sugar in the three patients treated

Fig 5

Fig 6

Fig 7

Fall in globulin to normal a change noted in all cases
Congo Red Tests unchanged
Fig 8—July 27—end of first course
Note rounding of face
Fig 9—September 9—middle of third course
Marked rounding of face, double chin and redness of skin
Fig 10—October 7—23 days post treatment
Return to more normal appearance

This is the most marked instance of Cushing disease facies but both of the other patients developed the moon face prominent abdomen plethoric look and acne—even the 14 year old girl who was getting slightly inadequate doses The 6 year old boy developed a deeper voice a small amount of pubic hair, and questionable enlargement of his genitalia These undesirable effects seemed to be directly proportional to the size of the dose and inversely proportional

FIG 8

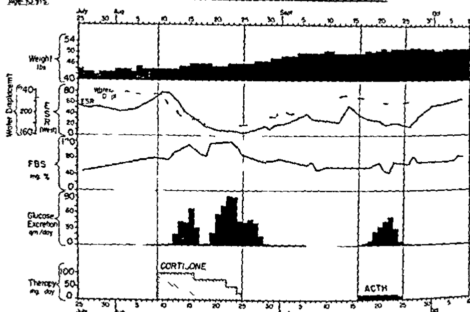


Fig 11

Cases 1 and 2 were still in remission 10 weeks after cessation of therapy Case 3 developed severe relapse again, after a fourth course of ACTH Cushing s facies have disappeared in Cases 1 and 2 Pubic hair is still present in Case 2 but the voice has normal pitch

DISCUSSION

DR CURRIER MCEWEN This slide (Fig 11) shows some of the effects noted in a 9 year old girl with juvenile rheumatoid arthritis (Still s disease) She had been sick for 8 months prior to August 1949, when cortisone was started During this time she had run a completely characteristic course for Still s disease, with involvement of multiple joints and loss in weight from 75 to 42 lbs As shown in the top horizontal column of Fig 11, weight began to increase within a few days of the start of cortisone and has continued Erythrocyte sedimentation rate and joint swelling decreased promptly, the former reaching normal in two weeks These data are shown in the second horizontal column of Fig 11 in which the swelling of one hand and wrist is recorded as the number of cubic centimeters of water displaced These evidences of clinical improvement were accompanied by disappearance of pain, return of ability to walk, increase in appetite and a general sense of well being

GLUCOSE TOLERANCE TEST

Vivian M age 10 yrs

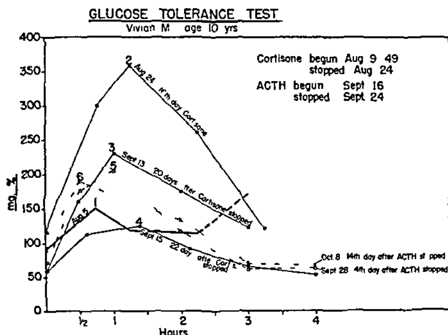


FIG 12

However there was one very noteworthy untoward effect As shown in the third and fourth horizontal columns of Fig 11 there was only a moderate rise in fasting blood sugar but there was striking glycosuria This began on the third day after the start of cortisone (in doses of 100 mg daily) and by the sixth day had reached 70 grams daily Because of this cortisone was reduced to 75 mg daily For two days there was little or no excretion of glucose in the urine but then in spite of continued reduction in the amount of cortisone the excretion of glucose rose again reaching a peak of 90 grams on August 22 When cortisone was discontinued the excretion of glucose gradually fell to normal in 5 days However as shown in Fig 12 the glucose tolerance curve which had become of diabetic type (curve 2) did not return to normal until 22 days after cortisone had been discontinued (curve 4)

After the discontinuation of cortisone on August 25 erythrocyte sedimentation rate and symptoms and signs promptly increased and the weight curve gradually leveled off By September 12 joint swelling was as severe as before treatment but it was considered unwise to resume hormone therapy until the glucose tolerance curve returned to normal By September 16 this had occurred and ACTH (Armour) was started in doses of 20 mg daily in 4 divided doses Even on this dosage sedimentation rate and symptoms decreased and weight began

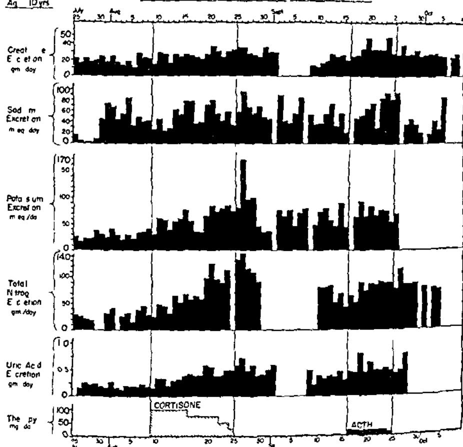


FIG 13

to rise again However glycosuria reappeared and became so pronounced that it was again deemed necessary to stop treatment At the present time studies are underway attempting to explain the mechanism of the glycosuria in this patient

Fig 13 illustrates the excretion of various electrolytes by this patient before during and after the administration of *cortisone* and of ACTH These changes are essentially the same as those reported by others

32

Observations on the Effects of ACTH in Patients with Rheumatic Fever and Rheumatic Carditis*

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HOUSE OF THE GOOD SAMARITAN (CHILDREN S MEDICAL CENTER) HARVARD MEDICAL SCHOOL BOSTON

This preliminary report will be divided into the following four sections (1) a summary of the clinical response of 11 rheumatic fever patients (2) observations on the skin reaction to the intradermal injection of hemolytic streptococcal vaccine (3) observations on the antistreptolysin O titer erythrocyte sedimentation rate and serum gamma globulin concentration, and (4) observations on sodium and potassium balance

1 CLINICAL EFFECTS OF ACTH (ARMOUR)

Clinical data are available on 11 patients treated with ACTH (Armour) Nearly all of the important manifestations of rheumatic fever are represented by these patients these manifestations include fever joint involvement subcutaneous nodules chorea signs of valvular involvement pericarditis congestive failure paroxysmal tachycardia, and elevation of the erythrocyte sedimentation rate The majority of the patients suffered from severe rheumatic fever and a high degree of active rheumatic carditis

In general the response to ACTH therapy was quite satisfactory in all but one of the 11 patients but the speed and extent of the response varied considerably Of 8 patients in whom treatment has been completed and who have been followed sufficiently long for evaluation 5 showed a prompt and striking improvement the disease becoming quiescent within a period of 4 to 10 weeks Two other patients still under treatment likewise have done exceptionally well so

* This study was supported by a grant from the Helen Hay Whitney Foundation Presented at ACTH Conference Chicago Illinois October 22 1949

far One patient who was desperately ill and in congestive failure became considerably better but still has low grade rheumatic fever another has reached the quiescent stage but her course was relatively slow while a third failed to show any definite improvement It is not possible to determine from the available data whether the observed clinical variations were due to differences in ability of the various patients to respond to the hormone or to differences in duration of treatment and variations in individual and total dosage of ACTH (Armour)

Although time does not allow for a detailed description of the effects of ACTH on all of the various rheumatic manifestations, it is of sufficient interest to point out that a definite mid diastolic murmur and an aortic diastolic murmur of moderate intensity in one early case and a moderately loud mitral systolic murmur and a definite mid diastolic murmur in another early case disappeared completely within three to six weeks while in a third patient with long standing mitral regurgitation a mitral mid diastolic murmur which developed in association with a recurrence of rheumatic fever again disappeared when the attack subsided In the last patient the systolic murmur as might be expected was not altered

Also of considerable importance and worthy of brief discussion is the effect of ACTH therapy on congestive failure associated with severe rheumatic carditis From our experience in four cases it would seem that the hormone has two opposing actions Either due to a direct antidiuretic effect of contaminating posterior pituitary lobe principles in the ACTH preparation or due to an indirect sodium retaining effect the administration of ACTH (Armour) tends to cause accumulation of fluids and hence aggravation of already existing congestive failure On the other hand suppression of the active rheumatic inflammatory process and consequent improvement in the myocardium tends also to improve renal function and thus relieve congestive failure The net result depends upon which of these two effects is the more pronounced and the more immediate When, in two of our patients congestive failure became worse in spite of a very low sodium intake we fortunately were able to control the situation with mercurial diuretics

When ACTH was withdrawn abruptly early in the course of treatment of patients with acute rheumatic fever an almost immediate rise in temperature and return of symptoms occurred, a result that was not surprising Of possibly greater significance was the reaction to gradual reduction in dosage and final omission of therapy In some instances this procedure was not associated with any untoward effect In others however relapses of varying severity were observed The interesting feature of these relapses was that in a number of instances

the fever rise in sedimentation rate, and other rheumatic manifestations again subsides promptly and failed to reappear even though the reduced ACTH dosage was kept constant or the hormone was omitted altogether

Except for increases in congestive failure and one instance of severe mental depression serious untoward effects from ACTH (Armour) have not been observed Glycosuria significant elevation of the fasting blood sugar and hypertension failed to develop in any of our 11 patients Relatively minor side effects consisted of acne and development of roundness of the face These two manifestations usually became apparent during the second to fourth week of treatment and lessened gradually after discontinuation of therapy In connection with the problem of untoward reactions it should be noted that in general our patients received relatively small doses of ACTH

Finally, and as a conclusion to this clinical review it should be emphasized that in a number of our patients attacks of severe rheumatic fever appeared to be terminated by ACTH (Armour) and that all signs of an active inflammatory process in the heart subsided There is therefore considerable promise that this therapy when given early in an attack of rheumatic fever may at least in some instances prevent heart damage On the other hand it also should be pointed out that the response to ACTH therapy was less dramatic in several of the cases and therefore on the basis of our small number of observations the possibility that this form of treatment may be ineffective in certain patients cannot yet be eliminated

2 OBSERVATIONS ON THE STREPTOCOCCAL SKIN TEST REACTION

The fact that a positive delayed type of reaction to the intradermal injection of streptococci and streptococcal products is obtained in a high percentage of active rheumatic fever patients is well known and is one of the evidences for the hypersensitivity hypothesis of rheumatic fever It therefore seemed of interest to determine whether the administration of ACTH causes any change in skin reactivity to streptococci The observations available for this report are relatively few and inadequate for any final conclusions

The tests were done by injecting intradermally 0 1 cc of a diluted saline suspension of heat killed group A hemolytic streptococci containing approximately 4 million organisms per cc Among 16 active rheumatic fever patients who had not received ACTH 13 gave definitely positive reactions which reached a maximum intensity in 24 hours Three of the patients whose tests had been positive were treated with ACTH 15 mg 4 times daily and then re tested during

the second day of therapy The repeat test was negative in one and positive in two of these patients One of the patients who had given a negative reaction to the initial test was also treated with ACTH and re tested during the second day of therapy His second test was definitely positive

This small number of observations suggests that ACTH (Armour)

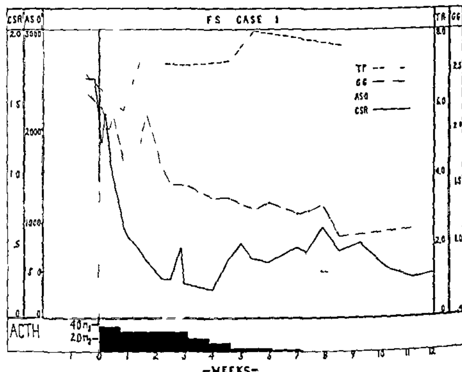


FIG 1 Effect of ACTH on serum concentration of total protein (R Pr) and gamma globulin (G G), and on the antistreptolysin O titer (AS O) and corrected sedimentation rate (CSR)

in the doses used does not have any immediate effect on the streptococcal skin reactivity in rheumatic fever We have not yet had the opportunity to study the effects of the more prolonged administration of this hormone

3 OBSERVATIONS ON THE ANTISTREPTOLYSIN O TITER, ERYTHROCYTE SEDIMENTATION RATE AND GAMMA GLOBULIN CONCENTRATION

The relationship of rheumatic fever to preceding hemolytic streptococcal infection and the consequent high level of circulating streptococcal antibodies in the early months of acute rheumatic fever

as well as the rise of streptococcal antibodies in association with rheumatic fever recrudescences are now well recognized (Fig 1) It is likewise known that streptococcal and other antibodies are largely concentrated in the gamma globulin fraction of the serum and that the gamma globulin concentration also rises in patients developing rheumatic fever following hemolytic streptococcal infection

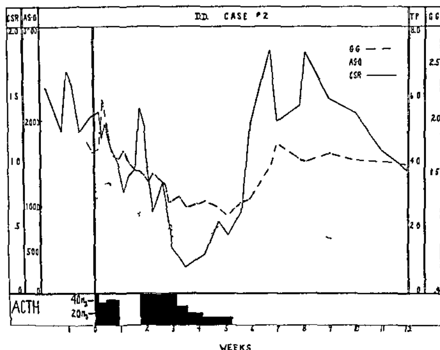


Fig 2 Effect of ACTH on serum concentration of gamma globulin (G G) the antistreptolysin O titer (AS O) and corrected sedimentation rate (CSR)

In spite of these known relationships the role of hemolytic streptococcal antibodies and of gamma globulin in the continuation of rheumatic fever is still not understood (Fig 2) Therefore with a view to shedding some light on the role of strepococcal immunity and increased gamma globulin concentrations in the mechanism of rheumatic fever observations have been made on the concentration of gamma globulin and the antistreptolysin O titer in patients treated with ACTH (Armour) These measurements have also been correlated with the erythrocyte sedimentation rate since the latter serves as a rough measure of rheumatic activity and also probably reflects changes in the concentration of plasma fibrinogen (Fig 3) Finally,

for control purposes the total serum protein has been measured in some cases

The gamma globulin concentrations have been determined by Kunkel's turbidimetric method

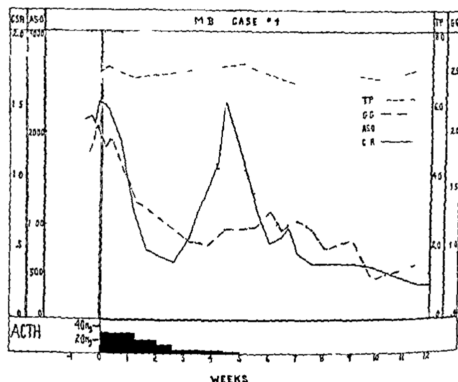


FIG 3 Effect of ACTH on serum concentration of total protein (T Pr) and gamma globulin (G G), and on the antistreptolysin O titer (AS O) and corrected sedimentation rate (CSR)

The results of our studies, illustrated in Figs 1–4, may be summarized as follows

a There was marked and rapid fall in the sedimentation rate beginning almost immediately after the administration of ACTH This fall in sedimentation rate closely paralleled clinical improvement

b The gamma globulin concentration which was distinctly elevated in all but one patient likewise decreased rapidly This change appeared to be independent of the total protein concentration which in general remained essentially stationary

c The antistreptolysin O titer followed the same pattern and became markedly reduced The rate of decreases in this antibody among 7 patients treated with ACTH was generally considerably more rapid

and on the average doubled that observed in previous years among a small group of controls who did not receive ACTH (Fig 4)

d As previously mentioned, discontinuation of ACTH was followed in some instances by clinical or subclinical relapses which were often transient in spite of no further increase in ACTH dosage In association with these episodes there was a rise in the sedimentation

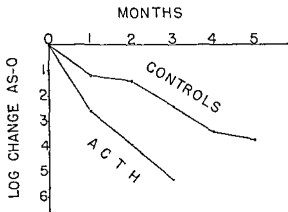


Fig 4 Average rate of decrease of antistreptolysin O titer (AS O) in 7 rheumatic fever patients treated with ACTH and in 9 controls

rate, sometimes to very high levels The gamma globulin concentration usually increased also but to a lesser degree while the antistreptolysin O titer appeared to be influenced very little

4 SODIUM AND POTASSIUM BALANCE

Our data on changes in sodium and potassium balances in rheumatic fever patients treated with ACTH (Armour) are still quite incomplete but are being reported because several of the patients seemed to respond in a direction opposite to that observed by others Furthermore the effect of ACTH on sodium excretion in those with congestive failure is of significance in relation to the practical problem of treating such individuals

In two extremely ill patients with congestive failure the administration of ACTH (Armour) caused a definite retention of sodium a decreased urinary volume and an increase in severity of the failure The addition of mercurial diuretics to the therapy as might be expected brought about a reversal of this condition with an increased excretion of sodium an increased urinary output and decrease in the signs of congestion

One other patient who was quite ill but who did not show definite

clinical signs of congestive failure likewise seemed to retain sodium when he was treated with ACTH (Armour) This transient retention caused no clinical difficulty

Other patients, not in congestive failure showed no striking change in sodium balance even though their clinical response to therapy was good

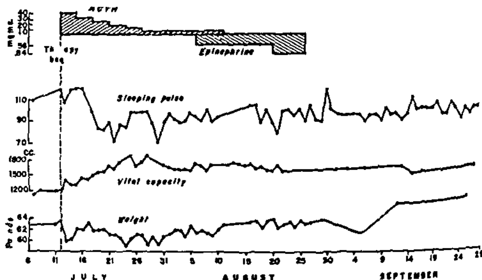


Fig 5

Finally and of especial interest is the observation of a definite sodium diuresis in at least two patients during the first 7 to 10 days of ACTH treatment This response, as previously indicated, is opposite to that reported by others in non rheumatic individuals

The changes in potassium balance were of a lesser order of magnitude than those observed with sodium and seemed to show no definite correlation with the sodium changes

DISCUSSION

DR H WAISMAN (Research Hospital and University of Illinois Medical School Chicago) We studied one case of rheumatic fever using ACTH in decreasing doses in the early part of the experiment and epinephrine in increasing doses in the latter part of the experiment to ascertain that epinephrine would accomplish the same effects as ACTH From Fig 5 you will note that the sleeping pulse decreased under ACTH and that the vital capacity increased without much white change Fig 6 shows a correlation of the eosinophil count under both ACTH and epinephrine with the sedimentation rate and the vital

capacity You will note that the sedimentation rate remained reasonably low even on very small doses of ACTH and rebounded a bit on epinephrine and then came down somewhat in the latter part of the experiment You will note that the eosinophil count escaped as the ACTH dose was decreased and as the patient was put on epinephrine

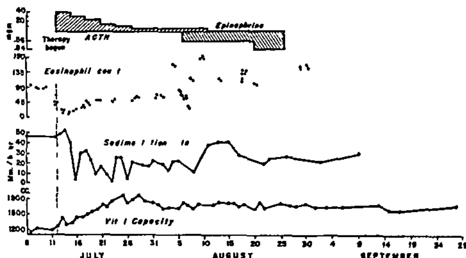


FIG 6

You will note that larger doses of epinephrine did not appreciably alter the eosinophil count

In Fig 7, you will note that there is no appreciable weight change although the vital capacity increased appreciably under ACTH therapy Likewise there was not much retention of fluid in the early part of the experiment although there was a tendency to diuresis on lower doses of ACTH which may correlate somewhat with the increased vital capacity

Fig 8 simply shows some hemo dilution under ACTH stimulation of the adrenal gland and shows clearly the marked change in the sedimentation rate under ACTH therapy which did not alter much on decreasing the dose The last figure (Fig 9) shows the electrocardiographic data for which there is insufficient time to go into details regarding the changes except that the PR interval did decrease as did the QT and the ECG rate

DR GEORGE W THORN I would like to make a practical suggestion In the management of these patients it is possible to decrease the excessive water retention restricting rigidly the water intake in pa

tients under ACTH therapy In addition, mercurial diuretics are useful although with a mercurial diuretic one may lose tremendous quantities of potassium Since potassium depletion is a serious complication of ACTH therapy, mercurial administration must be carried out cautiously unless supplementary potassium is given

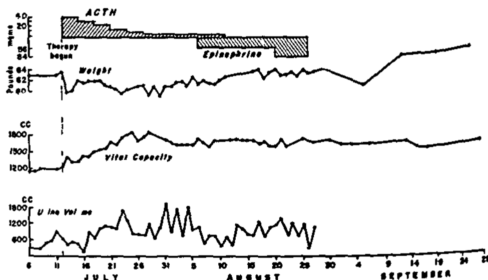


FIG 7

DR ALBERT DORFMAN I would like to state very briefly omitting any slides our experience with both rheumatoid arthritis and rheumatic fever

In a case of a 5 year old child with Still's disease our results have been essentially similar to those reported with the exception that we have observed this escape phenomenon particularly with respect to a marked eosinophilia and increase in sedimentation rate while on drugs, which then subsided and the patient had a good clinical remission

Concerning the rheumatic fever patients I should like to make several points One is that with patients with chronic rheumatic fever who have been inactive for a long time in two cases we have seen congestive failure develop on the drug but as Dr Massell has pointed out with the use of mercurial diuretics we have been able to continue the drug without any difficulty

I should like to point out that in our experience we can t quite share Dr Massell s enthusiasm of this being a cure In these chronic types of patients with the cessation of the drug the activity has returned

Finally, in both patients with rheumatoid arthritis and rheumatic fever we found a very marked decrease in the nonspecific hyaluronidase measured by the technique we have previously described

DR MAY G WILSON I can sympathize with Dr Massell s enthusiasm I cannot agree that he has presented evidence that we have a cure for rheumatic fever The physical signs of changing murmurs as everyone well knows are very common during active carditis and unless you have post mortem evidence that there was no damage you cannot consider that the valvular deformity had disappeared because the murmur was no longer present

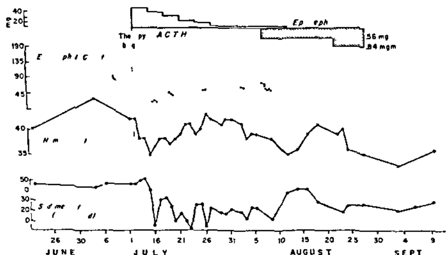


Fig 8

DR JOSEPH J BUNIM (New York University College of Medicine New York City) We have studied a patient who developed his first attack of rheumatic fever on June 1 8 weeks before admission An x ray taken at this time showed the heart to be normal in size and contour Five weeks after the onset apical systolic and diastolic murmurs were present On admission to Bellevue Hospital these signs were confirmed and x rays of the heart showed marked enlargement In addition a loud pericardial friction rub was heard over the precordium which persisted up to the day before Cortisone was begun A solitary subcutaneous nodule was found and removed for histological examination before therapy was begun

From Fig 10 several points will be noted

1 Administration of Cortisone and ACTH was associated with a fairly prompt fall in fever and erythrocyte sedimentation rate

2 There was, however, no reduction in the heart rate, which ranged around 140 per minute, when Cortisone was given With ACTH, the rate fell to levels of 90 per minute, but by that time the patient was in the fifteenth week of his illness

3 Despite Cortisone therapy, mercuhydrin was necessary on August 20 and September 7 because congestive failure associated with sodium retention became progressively more severe and the patient's condition was critical

4 Prior to and after administration of Cortisone no detectable amounts of sodium were present in the urine, until mercuhydrin was

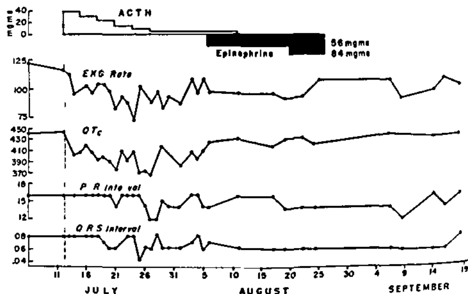


FIG 9

given (August 20) From August 31 to September 7 urine collections were not made On September 8 no sodium was found in the urine voided from 9 A M to 5 P M At 5 P M mercuhydrin was again given with a fairly good diuretic response The following day ACTH therapy was begun No further injections of mercuhydrin were necessary

5 It will be noted that for the first 6 days of ACTH therapy there was no urinary excretion of sodium

Our general impression is that in this one case Cortisone and ACTH may have contributed towards effecting a subsidence of the inflammatory reaction in the tissues of the heart At the end of therapy however (October 10), the patient's heart still showed moderate enlargement both to the right and left and the apical systolic and diastolic murmurs remained unchanged

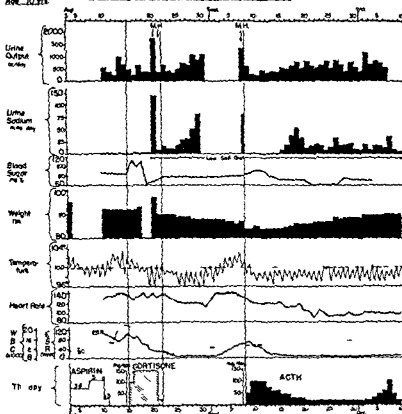


FIG 10

DR J F DWAN (University of Minnesota Minneapolis) It is going to be difficult to evaluate the clinical response to ACTH (Armour) in rheumatic fever Those of us that have seen a few cases however have been greatly stimulated by the apparent speedy recovery I am sure it will be necessary to have some biochemical evidence of response to therapy before we can accept the value of ACTH in this disease

Kelley Good Glick and McQuarrie in our department have papers in the press now on the mucoprotein levels and *non specific* hyaluronidase levels in rheumatic fever Their figures show a definite elevation during this disease process with a slow return to normal levels with the onset of recovery In the one case of rheumatic fever that we had the opportunity to study carefully through the kind offices of Dr Slocumb at The Mayo Clinic we noted a distinct drop in these levels following ACTH therapy This drop in the mucoprotein levels

and hyaluronidase inhibitor level paralleled an excellent rapid clinical response This observation is doubly interesting because Dr Mc Quarrie has just reported that in his series of cases of hypoglycemia, an increase was noted in the mucoprotein level following the administration of ACTH It is hoped that we can follow up these observations with more cases

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The Effect of ACTH on Rheumatic Children*

H N Helper R Lubschez K Hain and M G Wilson

NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL COLLEGE NEW YORK CITY

A summary of the effect of the administration of 40 to 50 mgm of ACTH (Armour) in equal divided doses every 6 hours for 4 24 hour periods is graphically presented in Figs 1 and 2 Three boys 9 to 10 years of age, selected for study include H W a well boy who had been followed from birth E M a rheumatic patient who has had no activity for the past 2 years and J A a patient with acute severe rheumatic carditis of 4 days duration

J A showed progressive signs and symptoms of severe carditis associated with slight pains in the left ankle and widespread erythema multiforme for 4 days prior to receiving ACTH The electrocardiograms revealed elevated ST segment and 3 1 heart block which returned to normal before the administration of ACTH The vital capacity dropped from his normal value of 2100 cc to 1100 cc rising to 1600 cc at the end of the experimental period There was marked clinical mprovement and the patient did not appear ill for 4 days following withdrawal of ACTH However 2 days after withdrawal the erythematous eruption returned and the temperature ranged from 37° to 39 5° C (Fig 1)

The patient showed clinical improvement before ACTH was given *During this control period the circulating eosinophil counts* ranged from 10 to 30 per cubic mm If it is postulated that a drop in circulating eosinophils following ACTH administration is evidence of increased adrenal secretion it would appear that this patient was able to respond to the stress of his illness

It is of interest that in 5 out of 6 patients with acute carditis the circulating eosinophils ranged between 13 to 97 per cu mm In all of these patients the Thorn test was within normal limits †

All of these patients were on the pavilion of the New York Hospital The hematological and chemical studies were conducted for a

These studies were aided by grants from the Commonwealth Fund and the Helen Hay Whitney Foundation

† Hain K and Wilson M G Immunologic and biochemical studies in infants and children with special reference to rheumatic fever VIII Response to pituitary adrenocorticotrophic hormone (ACTH) *Pediat* 4 579 Nov 1949

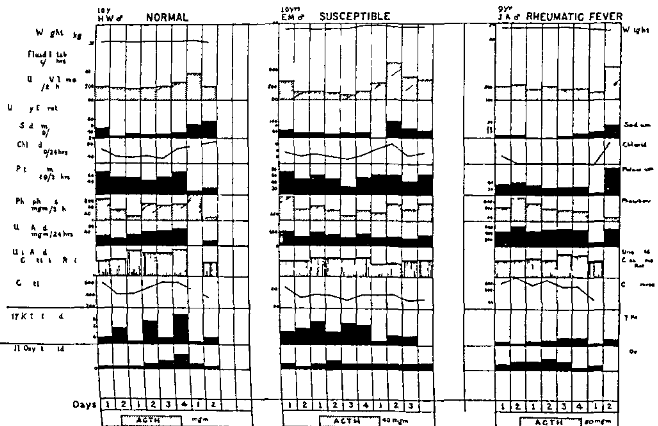


Fig 1 Effect of ACTH on children The 11 oxysteroids were calculated as per mg of formaldehyde For comparison with other values they have been recalculated as mg of cortin (See p 421 *)

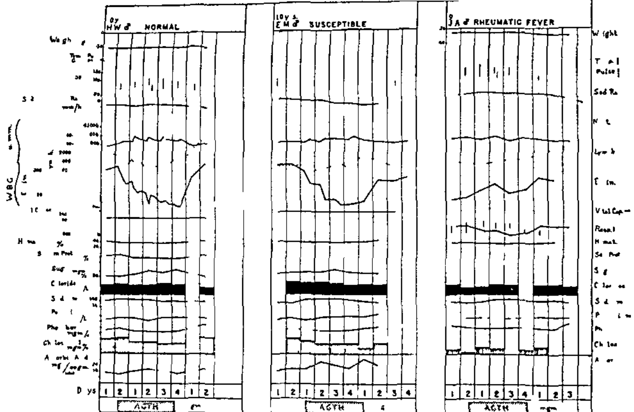


Fig 2 Effect of ACTH on children The neutrophil and lymphocyte counts were calculated per 2 cu mm

* The new absolute values are
(for *H H* 1 5 1 1 3 5 1 and 1 mg of cortin per 24 hours)
(for *F M*, 1 4 1 2 and on all successive readings 1 m cortin per 24 hours)
(for *J* 1, 1, 2 2 3 2, 2, 1 1 and 1 mg cortin per 24 hours)

control period of 2 to 4 days before and after the 4 day experimental period The children were on a constant calculated diet and a fluid intake limited to 1000 to 1200 cc per day There were no side reactions or untoward symptoms referable to the administration of ACTH during the experimental period

A comparison of the hematological and metabolic changes noted in the 3 patients is of interest However, interpretation of any differences observed cannot be made on such limited data The following observations perhaps merit comment In the rheumatic inactive patient the eosinophil count did not return to normal in the control period In the patient with active rheumatic carditis the initial eosinophil count was significantly lower than normal prior to administration of ACTH (Armour) and remained at low levels during the experimental and second control periods The sedimentation rate in the inactive rheumatic patient who had a respiratory infection fell to normal on the third day following administration of ACTH In the patient with active carditis the sedimentation rate remained elevated throughout the experimental period

The blood chemistries remained relatively stable, similar to observations reported in adults The ascorbic acid in the white blood cell platelet layer revealed an upward trend In 2 patients the serum cholesterol level fell during ACTH administration

Forty eight hours following the discontinuance of ACTH there was a marked diuresis in all the patients The changes in urinary electrolytes during ACTH administration were similar to those reported for adults having comparable treatment except that chlorides were significantly decreased in the patient with active carditis The creatinine excretion did not remain constant during administration of ACTH although urine was collected for 24 hour periods Interpretation is limited since it is well known that creatinine excretion varies in children

The 17 ketosteroid excretion increased in all the patients during the administration of ACTH (Armour) The 11 oxysteroid excretion remained relatively constant in the inactive and active rheumatic patients

It is obvious that the accumulation of considerable data is necessary before the responses of children to the administration of ACTH or the mechanisms involved can be ascertained

DISCUSSION

There was no discussion on this paper

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The Effect of Adrenocorticotrophic Hormone (ACTH) (Armour) on the Clinical Syndrome of Dermatomyositis

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PRESBYTERIAN HOSPITAL COLLEGE OF PHYSICIANS AND SURGEONS COLUMBIA UNIVERSITY NEW YORK CITY

Dermatomyositis is a disease with a vague, poorly defined symptomatology is diagnosed chiefly by exclusion but evidently be longs in the group of the mesenchymal diseases together with lupus erythematosus disseminatus periarteritis nodosa, etc The onset is usually gradual There is an inflammatory process throughout the skeletal musculature characterized by lymphocytic infiltrations in the interfibrillar spaces with varying degrees of morphological changes in the muscle fibers themselves With it there may be associated certain changes in the skin an ill defined dermatitis or edema of the sub cutaneous tissues Sedimentation rate is usually elevated and there may or may not be an increase in serum globulin Symptoms are char acterized by weakness of various muscle groups with particular pre dilection for the muscles of deglutition the extraocular muscles and those of the thighs

We have treated 2 cases of dermatomyositis with ACTH (Armour), one for 18 days (Fig 1) and a second case for 9 days In the first case, symptoms of muscular weakness were present for a period of over 3 years Physical examination was negative save for an easily palpable spleen There was an elevated serum globulin (4 6 gm %) and the sedimentation rate ranged between 75 and 100 mm per hr (Westergren) The cephalin flocculation was positive and muscle biopsy from the vastus lateralis showed lymphocytic infiltra tions in the interfibrillar spaces between the myofibrils The treat ment with ACTH (Armour) is shown in Fig 1 Subjective changes during treatment were obscured by the mental reaction which will be discussed in another paper by Drs Hoefer and Glaser but she did note a marked increase in weakness of the left arm and leg without re

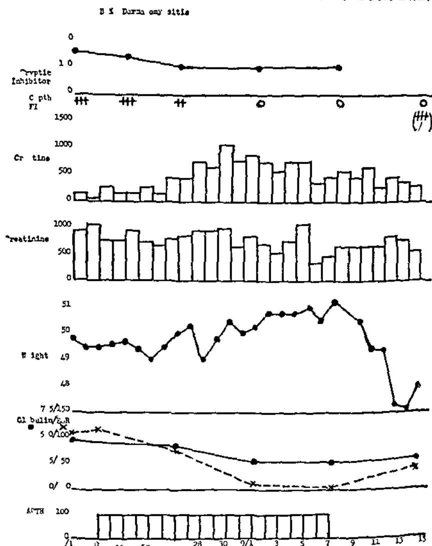


FIG 1 Tryptic inhibitor—mg equivalent to crystalline soya bean inhibitor when equal amounts of crystalline soya bean inhibitor and crystalline trypsin neutralize

Creatine and creatinine—mg per 24 hours
Weight—Kg
Globulin—Gm %
ESR—mm per hour
ACTH—mg per 24 hours

flex changes After 18 days of treatment with ACTH (100 mg a day), the spleen could not longer be felt, the sedimentation rate had fallen to normal—7 mm per hr —and serum globulin had decreased to 2 5 gm % the cephalin flocculation had become negative and a bi

opsy of the opposite vastus lateralis taken at the end of treatment showed no evidence of cellular infiltration in the interfibrillar spaces Two days following cessation of therapy her mental status cleared to the point where she was able to note subjective changes For a week after ACTH was discontinued she had no complaint of muscular weakness Twelve days following cessation of therapy with ACTH, the spleen was palpable the sedimentation rate had risen to 50 mm per hr cephalin flocculation had again become positive and she again noted weakness of the muscles of deglutition and of the intercostal muscles During the treatment period she showed a rather marked creatinuria for a time

The second patient was also a woman who had had weakness of the extraocular muscles manifested by diplopia intermittent in character for a period of 2 years She had also complained of weakness of the muscles of her legs which made it difficult for her to walk on her heels and to climb stairs Intermittently she had had a rash on her lower extremities which was macular with some thickening of the skin The sedimentation rate ranged between 80 and 85 mm per hr (Westergren), serum globulin was elevated (4 0 gm %) cephalin flocculation was negative but thymol turbidity was 3+ Biopsy of muscle of the thigh showed lymphocytic infiltrations in the interfibrillar spaces and a thinning of the superficial layers of the skin It is of interest that there was some myasthenic component in this patient since she demonstrated objective improvement in muscle power namely ability to walk on her heels after the injection of 1 mgm of prostigmine on two separate occasions She received ACTH (Armour)—100 mgm a day—for 9 days After the third day she experienced no further diplopia and after the fifth day she was able to walk on her heels and climb stairs with no evidence of weakness However the next day (the sixth of ACTH therapy) she began to complain of progressive and alarming weakness in the muscles of the extremities and the hormone was discontinued on the ninth day of treatment There was no return of diplopia Her sedimentation rate fell from 86 to 22 mm per hr in this 9 day period

Evidently the process which led to changes in proteins including globulins sedimentation rate and cephalin flocculation was controlled while on ACTH There was temporary control of symptoms of muscle weakness but these became intensified as treatment continued When muscle weakness was marked the serum potassium was lower than in the pretreatment period (4 2 to 3 5) but not at levels usually associated with paralysis Administration of potassium chloride by mouth did not materially change the symptoms of muscle weakness

In the first patient following withdrawal of the hormone symptoms of muscle weakness were temporarily benefited However in this

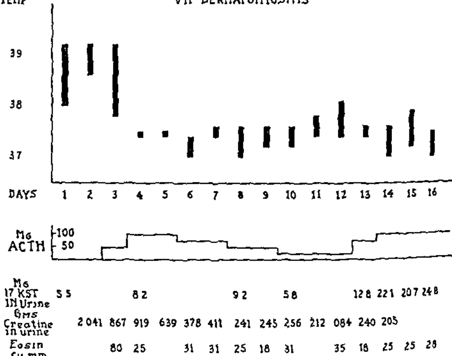


Fig 2 Effect of ACTH on the temperature, total number of eosinophiles and the urinary outputs of creatine and 17 ketosteroids of a patient with severe exacerbation of dermatomyositis

same patient after a period of time the muscular symptoms returned as did the protein changes which probably represent the host response to the abnormal process This pattern of response of muscle weakness to ACTH (Armour) is similar in our experience to that seen in myasthenia gravis However the protein changes are not characteristic of myasthenia and the histological changes in the skeletal musculature are more marked than the isolated lymphorrhages described in myasthenia

DISCUSSION

DR A T MILHORAT A brief word about a case of dermatomyositis studied with Dr T W Oppel

A patient aged 30 with very severe exacerbation of dermatomyositis displaying all the acute and severe manifestations of the disease with pain and tenderness so severe that large doses of demerol and frequent nerve blocks did not suffice to control the pain was given ACTH After 25 mgs there was a definite diminution in symptoms



Fig 3



Fig 4



Fig 5



Fig 6

After 50 mgs the pain and tenderness had quite subsided, and after 2 days of ACTH in doses of 100 mgs a day, practically no symptoms of the disease remained (Fig 2) With further treatment all manifestations of the disease disappeared The patient was entirely well 2 months after ACTH had been discontinued

DR HARRY SHWACHMAN I have some photographs of a patient treated at the Children s Medical Center of acute leukemia with dermatomyositis that showed a most dramatic improvement with ACTH therapy

Fig 3 shows the leukemia patient before the onset of antifolic therapy

Fig 4 shows the child before ACTH therapy

Fig 5 shows him on August 10 8 days after the beginning of ACTH therapy

Fig 6 is dated August 20 at the end of ACTH therapy

Fig 7 is one month after the beginning of ACTH therapy The child is still as appears in this photo



FIG 7

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Effects of ACTH in Patients with Collagen and Allied Diseases

J R Elkinton A D Hunt Jr L Godfrey W McCrory A Rogerson and Joseph Stokes Jr

UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE PHILADELPHIA

Effects of treatment with Armour s ACTH in 8 patients are reported The diagnoses were as follows juvenile rheumatoid arthritis disseminated lupus erythematosus dermatomyositis acute rheumatic fever and status asthmaticus The following metabolic measurements were done during at least part of each case study total circulating eosinophils serum concentration of sodium potassium and chloride balances of sodium potassium and total nitrogen urinary excretion of corticoids and 17 ketosteroids Measurement of the uric acid creatinine ratio and assay of serum anti hormone activity were made in the one case (E B) who appeared to become refractory to ACTH

Results of treatment were as follows

Acute Rheumatoid Arthritis

W H 5 year old male received 25 mg ACTH per day for 7 days (see Fig 6) Temperature dropped abruptly to normal joint pain disappeared and joint swelling subsided Following withdrawal of ACTH signs and symptoms returned despite the administration of epinephrine No further treatment was attempted B G 9 year old female received ACTH intermittently over a period of 148 days patient s signs and symptoms were relieved with an initial daily dose of 40 mg ACTH (Fig 1) As treatment progressed increase in dosage up to 75 mg was required to maintain the remission Acne hirsutism and oily hair appeared suggesting an early Cushing s syndrome ACTH therefore has just been discontinued

Disseminated Lupus

N H 15 year old Negro female with typical disseminated lupus proven by skin biopsy received 100 mg per day of ACTH for the

first 3 days with diminishing doses thereafter (Fig 2) ACTH was discontinued on the fifty second day with apparently complete remission to the present time (3 weeks thereafter) E B, 29 year old white female with subacute joint swelling for 8 months developed fever anemia splenomegaly 6 weeks before admission for study at which time she appeared moribund Patient responded to ACTH in

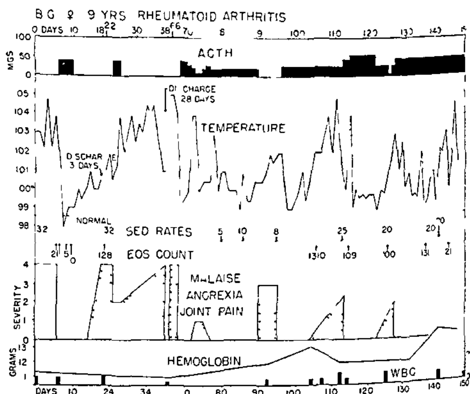


Fig 1

daily doses of 75 mg fever subsided and anemia improved (see Figs 3 and 7) After 6 weeks intermittent therapy of doses as high as 200 mg patient became refractory temperature rose red count fell pleural and pericardial effusions appeared and death occurred on the seventy eighth day of study

Dermatomyositis

M F 5 year old male, with this diagnosis supported by skin biopsy, developed high fever skin rash and edema on penicillin therapy 7 weeks prior to study On admission was moribund responded progressively to several courses of ACTH therapy, 40 to 80

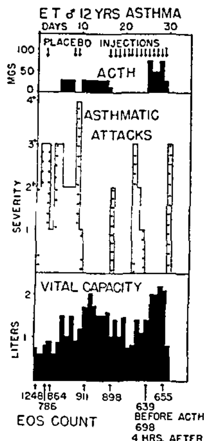
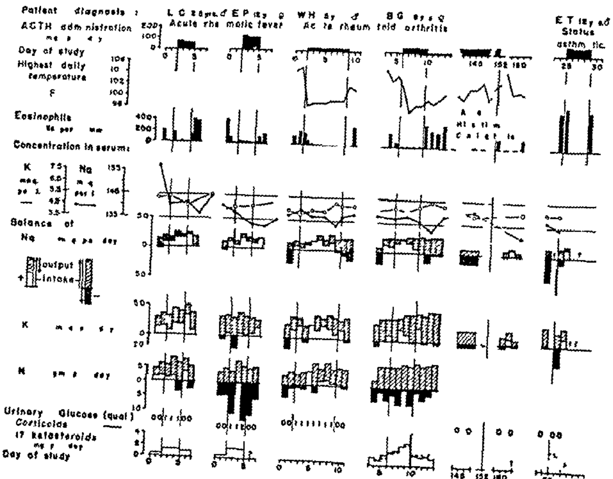


Fig 5

third complication was the refractory state developed by E B, with fatal results The evidence is not unequivocal as to whether this state was due to an antihormone to adrenal exhaustion, or to inability of the end organs to respond to adrenal steroids

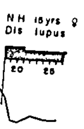
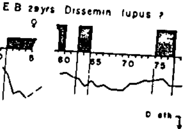
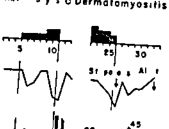
DISCUSSION

There was no discussion on this paper



Patient diagnosis
ACTH administration
Day of study
Highest daily temperature
F
Eosinophils
Concentration in serum
K
Na
Balance of
Na
output
intake
K
N
Urinary Glucose (qual)
Corticoids
17 ketosteroids
Day of study
Acute rheumatic fever
Status asthmaticus

Fig 6

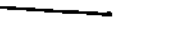


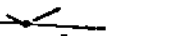




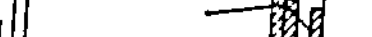








ACTH administration
Day of study
Highest daily temperature
F
Eosinophils
Concentration in serum
K
Na
Balance of
Na meq per day
output
intake
K
N
Urinary
Glucose (qual)
Corticoids
17 ketosteroids
Day of study
M.F
Dermatomyositis
E B 29yrs ♀
Dissemin lupus
N H 15yrs ♀
Dis lupus
CO₂
mM/l
Death

Fig 7

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The Effect of ACTH on One Case of Periarteritis Nodosa *

Ralph Goldman William S Adams William S Beck Melvin Levin and Samuel H Bassett
VETERANS ADMINISTRATION CENTER LOS ANGELES
and
Abraham White
UNIVERSITY OF CALIFORNIA LOS ANGELES

A patient with periarteritis nodosa was chosen for metabolic studies of the effect of ACTH because this disease is considered to be one of the collagen diseases and ACTH has been reported to be effective in this group In addition we were curious to determine the effect of ACTH on the very high eosinophil count observed in this patient Since our studies to date have revealed no results at vari ance with the general effects of ACTH, our results will be sum marized as briefly as possible To our knowledge there is no previous report of treatment of a patient with this disorder with pituitary adrenocorticotrophin

The patient a 59 year old white male has had asthma for 4 years peripheral neuritis for 10 months and subsequent pains in the ex tremities muscle wasting and progressive weakness low grade fever and anorexia Laboratory examinations revealed mild albuminuria eosinophilia persistently above 15% and decalcification of the bones and advanced pulmonary emphysema Muscle biopsy was found to be consistent with the diagnosis (Figs 1 and 2)

Method of Study

The patient was studied in the Metabolic Unit where he was placed on a controlled diet which was calculated to contain 2200 calories with 75 grams of protein and which on analysis was

* Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration



FIG. 1 Photograph of the patient W K A taken 8 days after the initiation of ACTH therapy

demonstrated to have 11 6 grams of nitrogen Five day periods were used Periods 1 2 and 3 were control periods, during period 4 the patient received 0 2 unit of pitressin every 6 hours the amount contaminating our standard dose of ACTH during periods 5, 6 and 7 the patient received 10 mgm of ACTH subcutaneously every 6 hours and during periods 8 and 9 he was placed back on the pitressin schedule During period 2 he developed a severe attack of asthma and refused numerous feedings lost weight and went into negative nitrogen balance Equilibrium was apparently achieved during periods 3 and 4 During the fourth period the patient was under the impression that he was receiving the active hormone although, as previously stated he was receiving pitressin in small dosage This period indicated that

the balance achieved in periods 1 and 3 were approximately correct At present, we are prepared to submit data through period 6 and a few observations carried through period 8

Subjective Responses

The subjective response shown followed the now familiar pattern Over 5 days of pitressin there was no apparent subjective or objective

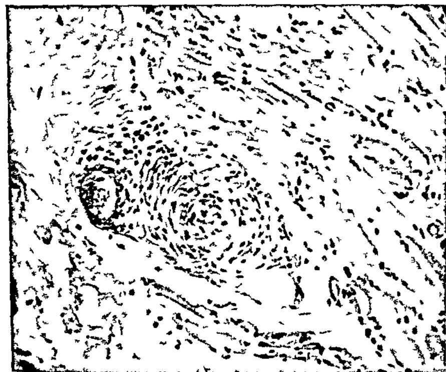


FIG 2 Photograph of a section of the muscle biopsy performed on patient W K A which established the diagnosis of periarteritis nodosa

change Since he believed that he was actually receiving ACTH at the time he expressed his disappointment at the results However on the day ACTH was started without the patient being aware that a different medication had been given there was within 6 hours a feeling of remarkable improvement and an incipient asthma attack had been aborted There was no true euphoria but the patient expressed a sense of well being and improved morale This continued until the ACTH was discontinued at which time there was a prompt symptomatic relapse After several days there was a rebound from the

deepest phase of symptomatic reaction, but the return to the treatment level was incomplete Pitressin was continued during the period of ACTH withdrawal

Objective Clinical Observations

Clinically only a few objective findings were noticed The patient s blood pressure which had averaged 110/75, rose to 130/85 for 3 days then returned to its base line When ACTH was withdrawn the pressure fell to 85 55 for 2 days before stabilizing again During the administration of the ACTH there was a gradual fall in the pulse

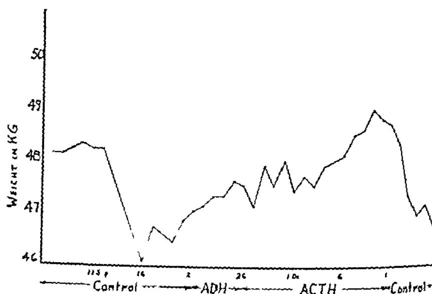


Fig 3 Changes in body weight accompanying the administration of ACTH

rate from 100 per minute to 70 The pulse rate returned to 100 within 4 days after discontinuance of the drug There was no response of the temperature to the initiation of therapy, but the rectal temperature fell from 99° to 97° in the 3 days following withdrawal and just as promptly returned to 99° Weight has been approximately stabilized at the level determined before the asthmatic attack when ACTH was initiated A weight gain of a little more than 1 kilogram followed despite a marked negative nitrogen balance The patient lost 2 kilograms in 4 days following the cessation of therapy (Fig 3)

Other signs of clinical improvement were an increase in the amount of peripheral vasodilatation, with improved color, definite clearing of the asthma marked reduction of sputum increased ability to move about and increased pinprick discrimination in the anaes

thetic areas Withdrawal of ACTH did not appear to result in complete regression, in the first 9 post treatment days of observation

LABORATORY DATA

Hematology

The hematologic response was as expected The eosinophils dropped from an average of 1250 per cu mm to 25 within the first

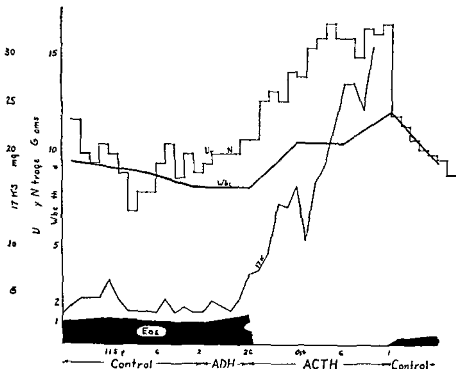


FIG 4 Effect of ACTH on circulating eosinophils Neutral 17 ketosteroids Total W B C count and urinary nitrogen

24 hours and after disappearing did not reappear until 24 to 48 hours after the drug had been withdrawn From the third to the ninth post treatment day the level fluctuated at 300 per cu mm The fall in the circulating eosinophils was more rapid than in the bone marrow The latter which averaged 23% in two aspirations performed before treatment fell to 7 6% on the second day of treatment but 0 8% were still found on the tenth day of treatment There was a small increase in the total white cell count in the peripheral blood during treatment (Fig 4)

Nitrogen Balance

The change in the nitrogen balance was striking There was a steady increase in the negative nitrogen balance for 7 days until the loss was one third greater than the intake, at which time the output levelled off This continued for the remainder of the 15 days that the patient was under treatment The nitrogen loss was via the urine since there was an actual decrease in the daily loss of fecal nitrogen Within the first 24 hours after the withdrawal of the ACTH the urinary nitrogen had fallen almost to pre treatment levels (Fig 5)

Chemical Observations in Blood Urine, and Sweat

The level of the blood glucose was not significantly altered although the glucose tolerance curve was 30% higher during treatment The glutathione level which had run somewhat high, fell 25% to within normal range There was no apparently significant change in

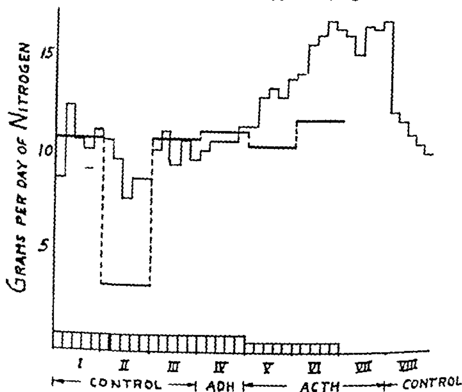


FIG 5 Nitrogen balance Periods 5 days Heavy black lines joined by broken lines indicate the level of nitrogen intake Fecal nitrogen is plotted at the bottom of the figure The irregular line intersecting intake denotes the sum of urinary and fecal nitrogen Nitrogen loss is depicted by extension of this line above that of intake

the serum electrolytes The serum creatinine and urine creatinine levels remained constant However, the serum uric acid fell from a pre-treatment level of 3 35 milligrams % to 1 25 milligrams % after 15 days of treatment This low level remained a full period (5 days) after ACTH was stopped The urinary uric acid rose from a level of 1 1 grams per day to a peak of 1 9 grams on the sixth day, and then gradually fell to subnormal levels continuing down to an average of 0 5 gram each of the 7 days after treatment (Figs 6 and 7)

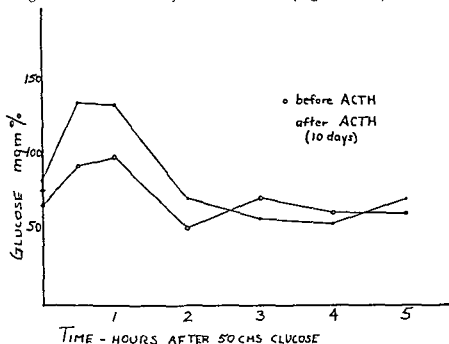


FIG 6 Effect of ACTH on glucose tolerance curve

A sweat test performed during the control period showed levels of 31 milli equivalents of sodium and 24 milli equivalents of chloride as contrasted with 6 milli equivalents of sodium and 2 5 milli equivalents of chloride after 15 days of treatment 17 Ketosteroids increased from an average of 4 milligrams per 24 hours to an average of 27 milli grams The *first day after cessation of treatment the value was* 13 3 milligrams and the second day was 5 7 milligrams the average for the succeeding 4 days was 6 5 milligrams

REMARKS

The prompt gain in weight on initiating therapy and its equally prompt fall when the hormone was discontinued are almost certainly

to be associated with changes in the volume of extracellular fluid These changes in weight, we believe, must be attributed to ACTH since the amount of pitressin contaminating our preparation was given during the pre and post control periods

The markedly negative nitrogen balance in an emaciated individual is distinctly disturbing, since, if long continued, it must ultimately lead to further severe depletion of the protein reserves One

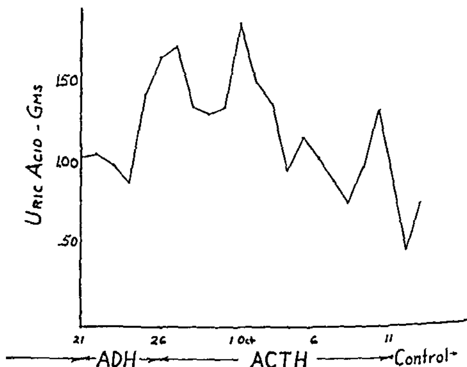


Fig 7 Daily excretion of uric acid in urine Note sharp rise in excretion of uric acid during first 6 days on ACTH followed by decrease to below level of control period

might speculate that the increased excretion of nitrogen indicates the resolution of inflammatory tissue and is therefore desirable, and, it is hoped self limited On the other hand if it represents the dissolution of some less vitally required body protein from which a substance essential to the well being of the organism can be fabricated, the ultimate outlook is unfavorable Obviously, more prolonged and careful studies of the various factors which may influence the nitrogen exchange are essential to a proper understanding of the action of the hormone

SUMMARY

In summary, this patient with periarteritis nodosa responded to ACTH by obvious improvement in well being His pulse rate de creased there were transient changes in blood pressure and tempera ture, and his weight increased during treatment The circulating eosinophils fell promptly but there was a less rapid response of the sternal marrow eosinophils Despite the nitrogen loss there was a persistent weight gain The blood glutathione was reduced, as was the serum uric acid There was an initial increase in the uric acid excretion but this decreased below normal before the ACTH was stopped and continued to decrease and then to level off below the

R.G 20 female 8510 Dx: Polyarteritis

Rx: ACTH 40 mgm/d for 9 d and 60 mgm/d for 12 d

Clinical Data	Pre-Rx	End of Rx
Orthopnea	++++	+
Hydrothorax	+++	+
Diastolic Gallop	+	0
Edema	++	+
Rt Radial N Paralysis	++++	+
Acne	0	++++
Appetite	poor	excellent

FIG 8

original base line after the ACTH was stopped The sweat test showed a marked fall in sweat sodium and chloride after 15 days of treatment and the urinary 17 ketosteroids showed an eightfold in crease

The symptomatic improvement pulse rate weight gain nitrogen loss plus 17 ketosteroids returned to pre treatment levels within a few days after the cessation of therapy The eosinophil count blood glutathione serum uric acid and urine uric acid were still below pre treatment levels 5 days after ACTH withdrawal

DISCUSSION

DR J SYDNEY STILLMAN I should like to present briefly the data on one case of polyarteritis nodosa treated with ACTH Our experience con firms that of Dr Goldman

The patient was a 20 year old married woman whose present ill

ness began about November 1, 1948 She developed rhinitis and a cough productive of yellow sputum She received for treatment a sulfonamide, the second time she had received this medication She subsequently developed fever dyspnea on exertion, asthma, orthopnea weight loss of 33 pounds marked weakness, pericarditis and peripheral neuritis Muscle and skin biopsy showed arteritis and arteriolitis consistent with polyarteritis nodosa Figs 8 and 9 show the changes noted after the administration of ACTH for 12 days

R G 20 Female 5510 Dx: Polyarteritis

Rx: ACTH 40 mgm/d for 9 d and 60 mgm/d for 12 d

Lab Data	Pre-Rx	End of Rx
Hematocrit	37	41
Sed Rate	0 8 mm/min	0.15 mm/min
WBC	16 000	12 000
Eosinophils	2 200	1
Vital Capacity	1.3 L	1 6 L
17 K to Steroids	73 mgm	18 6 mgm

Fig 9

The patient completed her course of treatment with ACTH on October 12 1949 During the past 8 weeks there has been evidence of a return of activity of her disease but of a considerably lower order of severity

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The Treatment of Scleroderma with Adrenocorticotrophic Hormone Preliminary Observations

Theodore B Bayles Carlyle F Stout J Sydney Stillman and Walter Lever

ROBERT BRECK BRIGHAM HOSPITAL PETER BENT BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

At the present writing 4 patients with scleroderma have been treated with adrenocorticotrophic hormone at the Robert Breck Brigham Hospital Three patients received a 3 week course of ACTH and one patient received 2 weeks of therapy

Epinephrine tests performed on these patients as well as 6 other patients with scleroderma at the Robert Breck Brigham and Peter Bent Brigham Hospitals were found to be normal indicating normal adrenal cortical function

Prior to treatment skin biopsies electrophorectic patterns of the blood protein complement levels blood volume determinations (Evans blue) bone marrow studies and 17 ketosteroid excretion were determined and these procedures were repeated on the last day of ACTH therapy

Reticulocyte counts were done daily for the first 15 days of treatment in three cases (2 3 4) Eosinophil counts were done twice weekly as were white blood counts and hematocrits

CASE REPORTS

Case 1

A G a 53 year old white housewife was admitted to the Robert Breck Brigham Hospital for the second time on August 19 1949 complaining of stiffness of the fingers pain in the phalangeal joints and inability to flex the hands

About 3 years before admission she first noted pain in the hands and knees and 6 months later a diagnosis of rheumatoid arthritis was

made Two years before admission she noted progression of her illness characterized by tightness and stiffness of the skin of the fingers associated with brownish discoloration She was admitted to this hospital at that time and a diagnosis of scleroderma was made In the past 2 years she continued to have stiffness and inability to flex the fingers and toes The skin of the face felt tight Tightness of the skin over the right ankle was noted with aching and limitation of motion of that joint

Physical examination on admission showed a well developed and nourished white woman Blood pressure 126/80 The skin of the face was somewhat tightened Over the dorsum of the fingers, the skin was smooth and taut, with only a few areas of wrinkling over the joints Over the dorsum of the hands and wrists this change was moderate and was also present over the right anterior tibial region There was patchy loss of pigmentation and hyper pigmentation over the involved areas There was slight impairment of motion of both wrists Flexion of the fingers was impaired, lacking about 2 centimeters of opposing the fingers to the thenar eminence of the left hand and about 1 centimeter on the right

A G 53 Female 3254 Dx Scleroderma

Rx ACTH 80 mgm/d–3 d 40 mgm/d–8 d 20 mgm/d–3 d.

	Pre Rx	End of Rx	3 wks Post Rx	6 wks Post Rx
Morning Stiffness	+++	0	++	+++
Joint Pains	++	0	+	++
Joint Mobility	poor	good	fair	fair to poor
Skin Tightness	+++	+	++	+++
Appetite	fair	excellent	good	good

Fig 1

Course (*see Fig 1*) After pre treatment data were collected, the patient was started on 20 milligrams of ACTH intramuscularly every 6 hours On the third day of treatment she was awakened at 3 00 a m with substernal oppression and a sensation of smothering which kept her awake the remainder of the night Physical examination showed no change and the electrocardiogram was normal The dosage of ACTH was cut to 10 milligrams 4 times daily On the fourth day of treatment the patient had gained 6 pounds weight her urine output was one half the fluid intake and she felt well The stiffness and tightness in her fingers toes and face were greatly improved and there was no pain in the ankle She was able to oppose the fingers to the thenar eminences Her appetite had improved tremendously On the eleventh day of treatment the dosage of ACTH was cut to 5 milligrams

every 6 hours and this dosage was continued 4 days when treatment was discontinued For 10 days following treatment the patient continued asymptomatic and then began to have a return of stiffness and pain in the ankle and stiffness and tightness in the fingers She did however, retain increased motion in the hands and her appetite was maintained Six weeks following, her condition was unchanged except that morning stiffness was increased

A G 53 Female 3254 Dx Scleroderma

Rx ACTH 80 mgm/d–3 d 40 mgm/d–8 d 20 mgm/d–3 d.

Lab Data	Pre Rx	End of Rx	3 wks Post Rx
Sed rate	0 35 mm/min	0 15 mm/min	
Hematocrit	40 8	40 6	
WBC	9 800	11 900	9,250
Eosinophils	49/cu mm	98/cu mm	85/cu mm
FBS	99 mgm	98 mgm	
17 Keto Steroids	6 6 mgm	6 6 mgm	

Fig 2

Laboratory Data (*see Fig 2*) Pre and post treatment biopsy specimens from the dorsum of each hand showed early changes of scleroderma There was no histologic change following treatment Blood complement was unchanged The gamma globulin was normal on admission and diminished almost 50% by the end of treatment (see Table 1) Corrected sedimentation rate fell from 0 35 millimeter per minute to 0 15 millimeter per minute Hematocrit was unchanged The white blood count rose from 9800 to 11 900 Eosinophils had an initial drop to 6 per cubic millimeter and rose to 98 per cubic millimeter on the last day of treatment 17 Ketosteroid excretion was unchanged There was a reticulocytosis of 3 1% on the eighth day of treatment Bone marrow examination showed a normal marrow prior to treatment and an erythroid hyperplasia at the end of the treatment There was no change in the number of eosinophils in the marrow and there were many mature neutrophils with a paucity of myelocytes juveniles and band forms

Case 2

F R a 37 year old married veteran was admitted to the Robert Breck Brigham Hospital for the first time on September 20 1949 with a history of scleroderma of 7 years duration In 1942 while in the Army he developed joint pains and was discharged with the diagnosis of arthritis Since that time he had intermittent pain and swelling of the fingers knees ankles and elbows Seven years ago he first noted

gradual increasing thickening of the skin of the fingers with increasing limitation of motion For the past 6 years he noted epigastric pain between meals relieved by food milk and soda In the past 6 years he complained of dysphagia with "sticking" of solid food in the lower part of the esophagus relieved by regurgitation Six years ago x ray of the upper gastro intestinal tract showed narrowing of the esophagus in the lower portion He lost 40 pounds in the past 6 years Three years ago he had 2 dilatations of the esophagus with relief of dysphagia for only 1 week

He was admitted to a Veterans Administration Hospital for the first time on June 3 1949 because of epigastric pain, stiffness of the fingers and blurring of vision At that time he was found to have severe fundal changes consistent with malignant hypertension the skin of the fingers was thickened and taut X ray of the upper gastrointestinal tract showed narrowing and ulceration of the lower part of the esophagus Barium enema showed extensive ulceration of the colon This was all felt to be on a scleroderma basis Esophagoscopy showed no esophageal lesion however He was treated with bland diet atropine, phenobarbital and discharged with the diagnosis of generalized scleroderma and hypertensive cardiovascular disease

He was admitted for the second time to a Veterans Administration Hospital on September 1 1949 because of breathlessness He had felt fairly well following discharge until 2 days before admission when he was awakened at night with extreme shortness of breath sensation of choking and fear of impending death He coughed up some pink frothy sputum He was taken to a hospital where the diagnosis of acute pulmonary edema was made Treatment consisted of oxygen tourniquets morphine and digitalis Electrocardiogram showed 'myocardial damage but no specific infarction He was transferred 2 days later to the Veterans Administration Hospital where the findings were essentially the same as on the previous admission Vital capacity was 1 8 liters Fundi were unchanged Blood pressure was 180/100 The changes in the skin of the fingers were the same On September 6 6 days after admission he complained of severe ' razor blade like epigastric pain X rays showed no evidence of esophageal rupture He was given a Sippy diet without relief He was transferred to the Robert Breck Brigham Hospital for ACTH therapy Physical examination on admission here showed scleroderma involving the peripheral two-thirds of the fingers and thumbs with limitation of flexion Blood pressure 155/95 Fundi not visualized Breath sounds prolonged in expiration at the lung bases with a few coarse crackling rales at the left base There was marked tenderness and splinting of the abdomen especially in the right upper quadrant Liver edge was felt 3 finger breadths

below the costal margin There was tenderness to percussion in the right upper quadrant

F R 37 Male 3512	D Scleroderma with esophageal stricture and coronary artery disease	
Rx ACTH 40 mgm/d for 16 d and 60 mgm/d for 5 d		
Clinical Data	Pre Rx	End of Rx
Dysphagia	++++ (fluids only)	++ (semi solids)
Epigastric pain	marked	mild
Finger flexion	very slight	good
Skin of fingers	thickened and tight	thickened and not so tight
ECG	left vent hypertrophy	normal

FIG 3

Course (*see Fig 3*) Patient was put on a Sippy regimen and after 4 days on this diet was feeling very well On September 28 1949 he was started on 10 milligrams of ACTH every 6 hours After 4 days of therapy he complained of epigastric burning associated with nausea and vomiting relieved momentarily by milk and cream However he had noted a marked increase in warmth of his fingers and increased mobility of the interphalangeal joints so that flexion was almost free He received epinephrine 0 5 milligram every 6 hours on the last two days of treatment The improvement noted in the skin of the hands continued to the time of discharge two weeks after cessation of therapy The dysphagia which was severe on admission and allowed ingestion of liquid only was considerably improved so that patient was able to eat semi solid food This improvement continued to the time of discharge

F R 37 Male 3512	Dx Scleroderma with esophageal stricture and coronary artery disease	
Rx ACTH 40 mgm/d for 16 d and 60 mgm/d for 5 d		
Lab Data	Pre-Rx	End of Rx
Sed Rate	0 45 mm/min	0 9 mm/min
Hematocrit	36	32
WBC	7 300	10 800
Eosinophils	114/cu mm	1/cu mm.
FBS	94 mgm%	138 mgm%
17 Keto Steroids	3 1 mgm	19 2 mgm

FIG 4

Laboratory Data (*see Fig 4*) Biopsies of the skin taken from the index fingers showed changes of advanced scleroderma with marked thick

ening of the collagen bundles and no inflammatory infiltration The sweat glands appeared atrophic and were tightly embedded in the sclerotic collagen There was no change in the histologic picture after 3 weeks of ACTH therapy Electrophoretic studies on the blood protein showed a slight increase in gamma globulin before treatment with a fall slightly below normal at the end of treatment (see Table 1)

Table 1

		A	a 1	a 2	B 1	B 2	Gamma	T P
Normal		3 74	34	61	1 02	34	75	6 80
Case #1	8-26	3 21	39	60	83	09	71	5 92
A G	9-16	2 81	39	54	89	13	35	5 12
Case #2	9-21	2 69	62	1 04	71	09	84	6 0
F R	10-12	2 83	74	1 30	74	07	70	6 38
Case #3	10-5	3 30	39	58	1 35	27	1 71	7 60
A Z	11-4	3 14	46	49	1 01	25	1 14	6 50

Complement was unchanged during treatment Stool guaiacs were persistently positive throughout the hospital stay Bone marrow studies showed an iron deficiency anemia with no hemosiderin in the marrow (probably due to persistent gastro intestinal bleeding) The eosinophil count fell from 106 per cubic millimeter to 28 per cubic millimeter on the first day and remained between 1 per cubic millimeter and 28 per cubic millimeter throughout treatment Sedimentation rate varied between 0 4 and 0 85 millimeter per minute during treatment The white blood count rose from 7,300 before treatment to 24,000 on the fourteenth day Fasting blood sugar rose from 94 milligrams % before treatment to 138 milligrams % at the end of treatment The electrocardiogram on admission showed the pattern of left ventricular hypertrophy At the end of treatment the electrocardiogram appeared normal, and 10 days following treatment showed low T waves in V5 and V6 consistent with left ventricular hypertrophy Excretion of 17 ketosteroids was 3 1 milligrams per 24 hours before treatment and 19 2 milligrams per 24 hours at the end of treatment Barium swallow showed no obvious change in the esophageal stricture following therapy

Case 3

A Z a 61 year old white female was admitted to the Robert Breck Brigham with scleroderma of 9 years duration In 1940 she

first noted pain and swelling in the hand joints In 1941 a thyroidectomy was performed at an outside hospital and she was thought there to have early rheumatoid arthritis or scleroderma In 1942 Raynaud s phenomena were first noted In 1944, at an outside hospital a diagnosis of scleroderma with Raynaud s syndrome was made In 1945 a gastric ulcer was demonstrated and esophageal changes consistent with scleroderma were also noted A skin biopsy in 1946 showed collagenous degeneration In 1948 a diagnosis was made of scleroderma involving the skin heart lungs and gastro intestinal tract She had mild dysphagia

Physical Examination On admission examination showed a cachectic white female who appeared older than her stated age The skin showed brownish pigmentation especially marked in the neck upper anterior chest forearms and hands There was marked cyanosis of the toes and moderate cyanosis of the fingertips The skin over the fingers hands and wrists was extremely tight shiny indurated and could not be wrinkled The skin over the forearms was moderately tightened as was the skin of the forehead The fingers were flexed and immobile There was atrophy and shortening of the fingertips Wrist motion was impaired as was motion of the shoulders neck and hips There was very little motion in the ankles The toes were fixed in flexion Radial pulses were absent bilaterally The heart was enlarged to percussion There was a Grade III harsh apical systolic murmur which had a buzzing character and was widely transmitted There were fine dry rales in the lung bases

AZ 61 Female #3o18 Dx Scl roderma
Rx ACTH 40 mgm/d for 21 days

	Pre R	E d of Rx	Post F
Pain	0	0	0
Jo nt Stiffness	++++	+++	++++
Skin T ght es	++++	+++	++++
Radial Pul es	bse t	full	absent
Dysphagia	++	+	++
Appet te	poor	good	poor

Fig 5

Course (see Fig 5) On October 11 1949 patient was started on ACTH 10 milligrams every 6 hours Within 4 days she was feeling much better having slight motion in the interphalangeal and metacarpophalangeal joints Both radial pulses were palpable and full The skin was loosened considerably especially about the fingers the wrists and the forehead There was increased warmth of the fingers and toes

The mouth could be opened more widely, the appetite was markedly improved and swallowing was less difficult

After 20 days of treatment the dosage of ACTH was cut to 5 milligrams 4 times daily and epinephrine 0 5 milligram every 6 hours was begun Following an injection of epinephrine she complained of palpitation and severe precordial pain with radiation to the neck left shoulder and forearm Physical examination revealed an acutely ill woman who was perspiring profusely Examination of the heart was unchanged except for a bigeminal rhythm ECG showed no evidence of myocardial infarction Epinephrine was discontinued The patient s chest pain subsided promptly

Within a few days after stopping ACTH therapy the skin became tightened, the extremities became cold, the radial pulses gradually disappeared, the appetite decreased, and trophic ulcers developed over the interphalangeal joints On discharge two weeks after treatment, she was very little, if any better than on admission

AZ 61 Female #3518 Dx Scleroderma

Rx ACTH 40 mgm/d for 21 days

	Pre Rx	End of Rx	Post Rx
Skin Histology	Scleroderma	Scleroderma	
Gamma Globulin	Increased	Decreased	
Complement	Normal	Normal	Normal
Eosinophils	Normal	Decreased	Normal
White Blood Count	Normal	Increased	Normal
Hematocrit	40	40	40
17 Keto Steroids	5 4 mgm	24 2 mgm	

Fig 6

Laboratory Data (*see Fig* 6) Biopsies of skin obtained from the thighs showed the late changes of scleroderma There was marked thickening of the collagen bundles In the upper third of the corium the collagen showed basophilic degeneration in many areas The elastic tissue in the upper corium was increased in amount and showed swelling and degeneration in many areas

The degenerative changes of the collagen and the elastic tissue were more pronounced in the specimen obtained after ACTH therapy

Electrophoretic studies before treatment showed a slight decrease of the albumin and a marked increase in the gamma globulin After treatment the albumin had increased and the gamma globulin had decreased (see Table 1)

The initial eosinophil count was 109 per cubic millimeter and fell to 40 per cubic millimeter in 4 hours Thereafter, the eosinophils ranged between 1 and 6 per cubic millimeter The count promptly

rose to 250 per cubic millimeter after treatment was stopped The hematocrit was 40 on admission and remained practically unchanged during treatment Corrected sedimentation rate was 1 2 millimeters per minute 3 days after treatment was stopped The white blood count numbered 5400 per cubic millimeter on admission, rising to 32 000 per cubic millimeter on the eighth day then gradually returning to normal levels during the course of therapy The fasting blood sugar was normal before and during treatment The 17 ketosteroid excretion was 5 4 milligrams per 24 hours before treatment and 24 2 milligrams per 24 hours after the 21 day course of ACTH therapy

Case 4

R S, a 36 year old divorced white female was admitted to the Robert Breck Brigham Hospital for the second time on October 4, 1949 because of scleroderma of 7 years duration In 1942 the patient noted swelling of a cut finger Soon the swelling had spread to involve all fingers of both hands Within 3 months of onset all joints of the body were affected with some swelling and pain and soon thereafter limitation of motion developed In 1943 she was hospitalized at another institution for 5 weeks and a diagnosis of arthritis was made From February 1944 to March 1945 the joint pains became worse She was admitted to the Robert Breck Brigham Hospital for the first time on October 16 1945 complaining of constant dull pain and stiffness of all joints including the spine and partial loss of motion of the mandible At that time the skin was tense and dry over the ears and nose and showed a brownish brawny desquamation The skin of the hands and terminal phalanges was tense hard and granular There were scattered areas of vitiligo All joints of the body showed some degree of ankylosis and tenderness The toes ankles and hands were most seriously involved and most painful The mouth could be opened only about 33% of normal Generalized muscular atrophy was present Treatment was supportive and the patient was discharged April 30, 1946, her condition unimproved She was seen at intervals in the follow up clinic and showed slow progression of her disease Aspirin did not relieve her pain During the two months before her second admission demerol administered daily was ineffective in controlling pain

System Review revealed that the patient had 6 upper front teeth extracted in 1947 in order to allow an adequate oral orifice For the past 6 years she has noted dysphagia She had no symptoms of Raynaud's syndrome

Physical Examination On admission examination showed a cachectic white woman lying stiffly in bed and appearing chronically ill Facies pinched Skin was tightened over the bridge of the nose over the

fingers, wrists and the distal portion of the forearms Over the toes both feet, the lower legs both knees, the scapulae and the thoracic spinous processes the skin was taut, shiny, and showed brownish pigmentation There were fairly well healed ulcers over the left patella, the left wrist and left elbow There was marked limitation of motion of the shoulders The fingers were fixed in extension and the thumb in flexion Lungs were clear Heart was normal Blood pressure 115/80 Femoral pulses good

R S 36 Female #2991 Dx Scleroderma

Rx ACTH 40 mgm d for three weeks then 20 mgm/d plus 2 mgm epinephrine/d for one week

	Pre Rx	End of Rx	Lost Rx
Pain	++++	0	+++
Skin Tightness	++++	+++	++++
Joint Stiffness	++++	+++	++++
Appetite	poor	good	poor
Dysphagia	+++	++	+++
Fever	0	0	+

Fig 7

Hospital Course (*see Fig 7*) Patient was given ACTH 10 milligrams every 6 hours from October 11 through October 31 1949 and then received 5 milligrams 4 times daily for one week On the second day of therapy the patient was free of pain had less difficulty swallowing and her appetite had improved On the sixth day of treatment she was able to move her fingers very slightly and could move the right wrist about 5 degrees Elbow motion had improved Subjectively and objectively the mouth could be opened more widely She was able to walk with assistance After 2 weeks of treatment the skin of the face was noted to be much looser and the motion of the wrists and fingers had increased slightly but was still minimal The appetite had improved tremendously The skin of the fingers wrists forearms and legs was loosened and easily wrinkled The patient gained 6 pounds in weight during the 4 weeks of ACTH therapy This gain was lost 2 weeks after treatment was stopped She was afebrile before and during treatment The day after treatment was stopped she developed a fever which ranged between 100° and 102° for 3 weeks Temperature then returned to normal

Laboratory Data (*see Fig 8*) Skin biopsy obtained from the lower legs showed late changes of scleroderma There was marked thickening of the collagen bundles in the corium and considerable fibrosis of the subcutaneous fat Many vessels showed marked fibrosis and thickening

of their walls There was no change at the end of treatment Electrophoretic studies of the blood proteins before therapy showed a slight decrease in the albumin and a marked increase in the gamma globulin After 3 weeks of treatment with ACTH the albumin had increased and the gamma globulin had decreased The hematocrit on admission was 37 6 the sedimentation rate was 0 95 millimeter per minute The white blood count was 6,800 The hematocrit rose to 42 2 after 3 weeks of treatment Sedimentation rate remained elevated and ranged between 1 4 millimeters per minute and 0 6 millimeter per minute The white blood count rose to 10 700 Eosinophils were 115 per cubic millimeter on admission and during treatment ranged between 4 and 184 per cubic millimeter most of the time numbering about 75 per cubic millimeter 17 Ketosteroid excretion was 7 0 milligrams per 24 hours before treatment and 15 2 milligrams per 24 hours at the end of treatment

P S 36 Female #[illegible]991 Dx Scleroderma

Rx ACTH 40 mgm/d for three weeks then [illegible]0 mgm/d plus 2 mgm epinephrine/d for one week.

	Pre Rx	End of Rx	Post Rx
Skin Histology	Scleroderma	No change	
Gamma Globulin	Increased	Decreased	
Complement	Normal	Normal	Normal
Hematocrit	37.5	42.2	4[illegible].0
Eosinophils	Normal	Normal	Normal
17 Keto Steroids	7 0 mgm	15 2 mgm	

Fig 8

SUMMARY

1 Four cases of scleroderma were treated with adrenocorticotrophic hormone for from 12 to 28 days

2 Clinical improvement during treatment was manifested by increase in appetite decrease in dysphagia weight gain loosening of the skin loss of pain increased mobility of joints and increased warmth of extremities (with return of radial artery pulsations in Case 3) In Case 1 substernal oppression occurred with a dosage of 80 milligrams of ACTH daily

3 The laboratory findings during treatment showed increased urinary 17 ketosteroid excretion significant decrease in gamma globulin no definite change in blood complement fall in circulating eosinophils significant increase in reticulocytes marked leucocytosis

and increased hematocrit in one case (Case 4) Bone marrow sections in Case 1 showed erythroid hyperplasia at the end of treatment Between the second and fifth day of therapy, there was a marked decrease in urinary sodium excretion, which returned to normal during treatment In Case 2, the electrocardiogram showed the pattern of left ventricular hypertrophy before treatment, became normal during therapy then reverted to its original pattern shortly after treatment was stopped Skin biopsies showed no histological change, except in Case 3 in which degenerative changes were more pronounced at the end of treatment

4 There was a return to pre treatment clinical and laboratory status, in all cases within 2 to 3 weeks of stopping ACTH therapy

5 Further hematologic data will be reported later

DISCUSSION

There was no discussion on this paper

38

The Effect of ACTH on Ulcerative Colitis

Charles H DuToit and Walter Bauer

MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

This patient age 47, had had mild ulcerative colitis for 5 years with a severe exacerbation 3 weeks before entry She was considered moderately to severely ill and was running a temperature of 102 to 103°

The pertinent information is presented in Fig 1 The x ray examination revealed the findings of a mild to moderately severe ulcerative colitis Proctoscopy confirmed this diagnosis The proctoscopic findings remained unchanged until 20 days of ACTH therapy when the mucosa appeared less friable Later it was less granular Marked improvement was apparent when therapy was discontinued At this time there was minimal or no disease There was however slight regression 5 days after cessation of therapy

The number of stools gradually decreased The character of the stool changed from liquid to mushy to semiformed

One notes that on the tenth day of therapy there was minimal edema of face hands and feet Later the patient developed a moon face acneiform rash buffalo hump hirsutism and pigmentation, of the type mentioned earlier by Dr Sprague

In Fig 2 one notes a rise in the serum CO and a fall in the serum potassium The other observed changes are readily apparent from the figure

In Fig 3 are recorded the fasting and 2 hour postprandial blood sugar The changes were slight

The serum phosphorus did fall The uric acid potassium creatinine ratios though not done regularly were not appreciably changed The serum uric acid did fall during the treatment period but one notes at the end when the dose was reduced this effect was in part worn off

The cholesterol and cholesterol esters increased as the patient improved This we interpreted as representing a better state of well being

The dosage of ACTH was reduced gradually and finally discontinued because of the excess weight gain the edema and what we

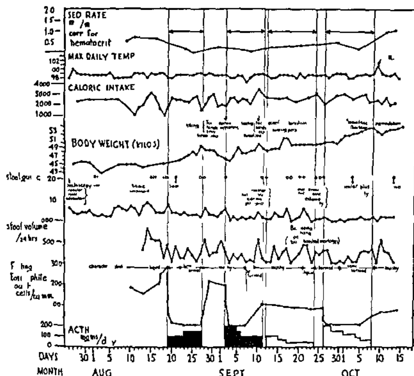
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5 Further hematologic data will be reported later

DISCUSSION

There was no discussion on this paper



SH 42yr ♀ Idiopathic Ulcerative Colitis 9mo Duration Abdominal Cramps Watery Diarrehea Wt Loss PE Neg Except For Slight Fever Lab Normal Except For loose Watery Stools 2to3+ Guaiac No Pathogens BA Enema Loss of Haustral Markings Protoscopic Ex Characteristic I U C

FIG 4

DR SEYMOUR J GRAY I want to say a word about the remarkable spontaneous remissions that occur in ulcerative colitis in which the mucosa returns essentially to normal and all symptoms clear up without any apparent explanation I wonder whether a large increase of adrenal activity or pituitary effect could produce this?

Another question I wonder about is the age of the patient Both of the e patients from their appearance were in the middle age group I wonder if a similar response would be effected in younger patients who have a much more fulminating form of ulcerative colitis

We always like to have some objective means to help us evaluate the clinical course of gastrointestinal disease Sodium and chloride and potassium, unfortunately do not help us You can imagine what

mindful of the ill effects of ACTH, and we must bear them in mind, particularly with long continued administration

DISCUSSION

DR GEORGE W THORN I would like to say just one word about the pigmentation

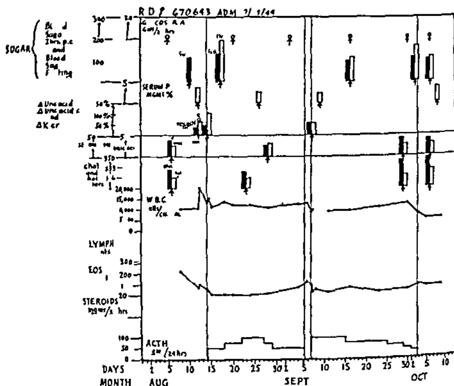
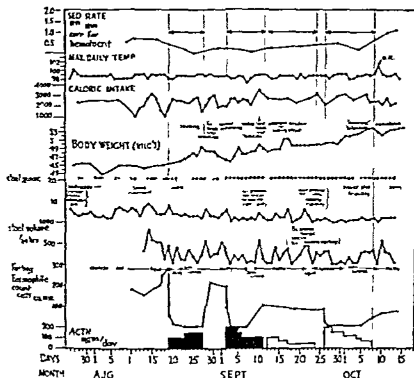


FIG 3 R D female—670643 adm 7/25/49

This increased pigmentation as described by Dr Bauer and Dr Sprague is a real change I think Dr Sprague s idea about the melanophore content of ACTH is very interesting

One of our patients with Addison s disease who had had 2 previous implants of pellets of desoxycorticosterone was given cortisone No pigmentation appeared At the sites of desoxycorticosterone implantation hyperpigmentation occurred with Compound E which we don t have to explain by means other than the steroid compound itself

DR WALTER BAUER I forgot to say that my lysozyme slide was broken this morning



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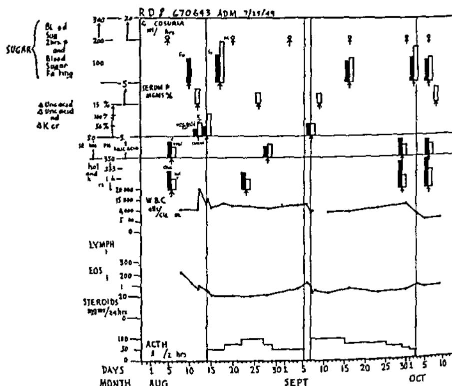


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day and have no *symptoms*, and consider themselves well We did not do a proctoscopy on that occasion

DR SEYMOUR J GRAY What dose did they have?

DR WALTER BAUER It got up as high as *200* in the first patient I must say the first patient was considered so ill by the gastroenterology service in our hospital that they thought we were playing with fire to



Fig 8

get this control data before starting ACTH and wondered whether she shouldn t have an enterostomy

DR SEYMOUR J GRAY *Did* the lysozyme titer fall?

DR WALTER BAUER I was just kidding

DR ROBERT F LOEB (College of Physicians and Surgeons Columbia University New York City) One word of caution about the interpretation of the lysozyme titer Dr Meyer and Dr Prudden showed increases of lysozyme titer in patients with ulcerative colitis They have now shown *that* granulation tissue itself may be a good source of lysozyme Therefore, interpretations of improvement in lysozyme may

be reflections of decrease in granulation of modification of the underlying disease process

DR THERON G RANDOLPH We have treated one 32 year old patient who had severe ulcerative colitis for a year and a half who, after a month of treatment first with 100 mgs and then 50 mgs after the first 10 days was found to react similarly to Dr Bauer s patients She

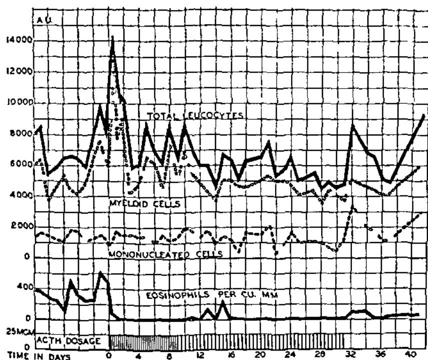


FIG 9

has been off the treatment 2 months and although she has relapsed somewhat she is at least 50% better than she was for a year and a half before treatment was started Her blood response to therapy is shown in Fig 9

DR WALTER BAUER I wish to impress upon you that in the second patient the proctoscopic examination never revealed a normal mucosa although we could wipe hard with cotton swabs and not produce any bleeding However it was still an obviously diseased mucosa The mucosa in the first patient was very close to normal

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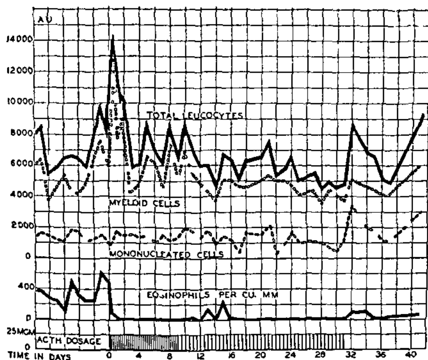


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DR EPHRAIM SHORR The suggested unfavorable effects have been hypertension I have noticed in none of the papers today any mention of hypertension

DR WALTER BAUER In our patients the hypertension was, at best slight

DR FREDERIC C BARTTER We treated a patient suffering from metastatic breast carcinoma with ACTH on two occasions On both occasions she developed hypertension On the first (see p 188) the hypertension was accompanied by marked salt retention During the second course of ACTH sodium intake was rigidly restricted so that salt retention could not recur but hypertension recurred nonetheless

DR WALTER BAUER We will have to close the discussion at this point

The one case of lupus erythematosus we have treated had skin biopsies done at regular intervals The first post treatment biopsy was done on the fourth day, and the changes were so near normal that our pathologist asked us why we hadn t done the biopsy at the end of the first 24 hours Dr Clark will comment on these sections later

39

Preliminary Report on the Use of ACTH in the Hypersensitive State

John E Bordley A McGehee Harvey John E Howard and E V Newman

THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL

Since Rich had shown that the basic anatomic lesions of rheumatic diseases could be produced experimentally by the induction of allergic reactions in animals [1] it was but natural to wonder whether the dramatic responses to cortisone and ACTH of rheumatoid arthritis and rheumatic fever [3] might not result from some change induced by these agents upon the mechanisms of hypersensitivity The rapid improvement which followed the use of ACTH (Armour) in a patient with exfoliative dermatitis from iodine a condition in which the same basic anatomic lesions have been described [1] furthered our interest We will discuss the results of therapy with ACTH (Armour) in 4 patients with lupus erythematosus disseminatus 7 patients with asthma and 2 with acute serum disease type of drug reaction

CLINICAL RESPONSE

The clinical course of the patients with lupus followed a distinctive pattern under the therapy Within 4 to 8 hours there was symptomatic and objective improvement in the acutely inflamed joints which were free of pain heat and swelling within 12 to 48 hours In the two more febrile patients there occurred at 12 and 18 hours drenching sweats with precipitous fall of temperature to subnormal levels much like the familiar crises of lobar pneumonia

The 7 patients with asthma were of the severe chronic variety 5 were thought to be of the intrinsic type 2 due to combined intrinsic and extrinsic factors When ACTH (Armour) therapy was begun all these patients had been in severe distress for months relieved only partially and briefly by the more heroic measures at present in vogue Their ages varied from 63 to 26 years duration of the asthma from 5 to 23 years Except for placebos all other medication was discon

tinued when ACTH (Armour) therapy was begun Unequivocal benefit was noted in from 4 to 48 hours All symptoms and signs had disappeared in from 2 to 7 days except in one patient 6 months pregnant who felt entirely relieved but in whom some rhonchi persisted Coincident with symptomatic relief tracings of the expiratory phase of respiration disclosed release from the relative obstruction to outflow

Two patients with severe penicillin reactions were treated One had fever arthritis and generalized giant urticaria the first manifestations of which developed 5 days after the initial dose of penicillin There was objective improvement in 4 hours and entire freedom from symptoms and signs in 18 hours The second patient had severe articular swelling with purpuric eruption 6 hours after a single injection of penicillin ACTH was begun the following day while the edema was rapidly increasing There was obvious objective improvement within 8 hours and all manifestations disappeared within 36 hours except for residual skin discoloration

DOSAGE SCHEDULES

All patients received the ACTH (Armour) on a 6 hour schedule the daily dose being divided and administered in 4 equal doses Three patients with lupus were begun on 100 mgm daily and one on 50 mgm the dosage being reduced to 20 mgm per day stepwise over periods ranging from 15 to 24 days One patient was continued on 9 mgm per day divided into 3 doses for a subsequent month of therapy

The patients with penicillin reactions were treated with 100 mgm per day in 4 divided doses for 2 days and then rapid reduction of dosage schedule to 20 mgm for a total duration of 6 and 5 days of therapy

Two of the asthmatics were begun on 100 mgm per day in 4 divided doses and one on 40 mgm in 4 divided doses for 4 and 5 days and this dose lowered stepwise to 20 mgm for total periods of from 9 to 20 days One patient was begun on 20 mgm per day, increasing the dose stepwise In this patient symptomatic improvement was noted on 30 mgm per day in divided doses which was the fourth day of treatment

In those patients with pale edematous polypoid nasal membranes the edema rapidly disappeared and the color became bluish pink Breathing space was greatly enlarged The lymphoid tissue when edematous likewise assumed a normal color the crypts became more prominent but there was no gross change in volume of the lymphoid tissue present In two patients there was complete obstruction of the

nose by polyps These began to shrink before the fifth day of treatment and entirely disappeared in one and almost disappeared in the other Three patients with antral clouding by x ray presented normal sinus x rays after ACTH (Armour) therapy

In several patients there were definite alterations in skin sensitivity to inhalent and bacterial antigens but studies to date are inadequate to warrant any conclusions

Four patients while on ACTH (Armour) and having good clinical response were tested for sensitivity to histamine All responded normally to intracutaneous histamine and likewise to intracutaneous curare both locally and by increased gastric flow of free HCl thus showing that *these tissues* at least can both produce histamine (or histamine like substances) and react to it in the normal fashion while the patient is under ACTH administration

RELAPSES

One patient with lupus has had complete remission of symptoms for a period of 4½ months It may be of significance that he was treated for 6 weeks with 9 mgm per day of ACTH after completion of his 20 day course of from 100 to 20 mgm per day Two of the lupus patients relapsed mildly and briefly after ACTH withdrawal One of these thereafter had a spontaneous remission the other had a second remission with another short course of ACTH only to relapse thereafter again for a brief period which then was followed by a spontaneous remission

UNPLEASANT SIDE EFFECTS

Most of these patients experienced mild euphoria at some stage of their therapy while others felt a restless and uneasy overactivity These feelings did not necessarily coincide with the dose level or the stage of treatment Some of the patients gained weight as much as 20 lbs and manifested general edema others gained no weight or even lost moieties of weight steadily Weight gain appeared at no uniform interval of time after treatment was started and there was no correlation between the amount of weight gained and manifest clinical improvement In some patients serum sodium and chloride concentrations rose in others fell Those with the sharpest chloride fall seemed to experience the most restlessness and uneasiness but some of these gained weight and some did not None of these patients manifested symptoms or signs of hypokaliemia Acne of a curious keratotic type seen by us previously only in Cushing s syndrome appeared over the forehead temples shoulders and neck in several of

the patients either toward the end of their therapeutic course of ACTH or a week or more after its cessation The acne gradually disappeared over several weeks

Fasting blood sugar rose 20 points or more in all the patients except 3, but no glycosuria appeared in any

SUMMARY

Results of therapy with ACTH (Armour) in patients with lupus erythematosus disseminatus asthma and drug hypersensitivity reactions have been sufficiently encouraging to warrant detailed investigation Certain striking tissue alterations in the nose and nasopharynx have been noted These effects of ACTH (Armour) on various manifestations of the hypersensitive state may offer leads as to the fundamental mechanism of its beneficial action

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DISCUSSION

DR ARTHUR J MERRILL After a 2 day control period a 54 year old white female practically moribund from disseminated lupus erythematosus was given 25 mg ACTH (Armour) every 6 hours for 9 days, then on the tenth and eleventh days 25 mg every 12 hours, after which the drug was discontinued The treatment period was followed by a 10 day control period Throughout the control and study periods the patient was maintained on a 2000 calorie tube feeding diet which contained 70 Gm protein 6 0 Gm sodium chloride, and with a volume of 2400 cc daily

The clinical response was quite dramatic with fall in temperature to normal (Fig 1), enhanced feeling of well being and subsidence of muscular and joint pains The improvement was maintained throughout the period of administration of ACTH, but within 24 hours after cessation there was beginning evidence of clinical relapse Relapse was not complete however until approximately 6 weeks after treat

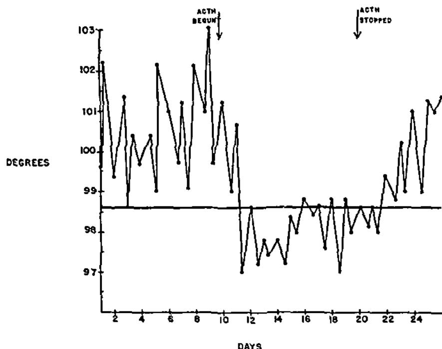


Fig 1

ment Wound healing of a biopsy site was not prolonged by ACTH (Armour)

The most striking effects noted in the laboratory were the hematological changes The reticulocyte count (Fig 2) which averaged 2 7% during the control periods abruptly rose to 10 9% on the fifth day of ACTH reached 16 8% on the ninth day, and fell to 7 6% on the fifth post treatment day remaining at 6 0% the other 5 days There was a rise in the hemoglobin concentration (Fig 3) of almost 2 0 Gm % by the eighth day of ACTH which was well maintained throughout the remainder of the study despite the fact that some 1500 cc of blood were bled from the patient for analysis The sedi

mentation rate fell promptly (see Fig 2) from control values of around 140 mm per hour to 80 mm per hour by the fifth day of ACTH administration, which continued until ACTH was stopped, after which the sedimentation rate rapidly rose to control level The total white blood count which had risen to about 16,000 per cu mm even before ACTH was begun remained at approximately this level throughout

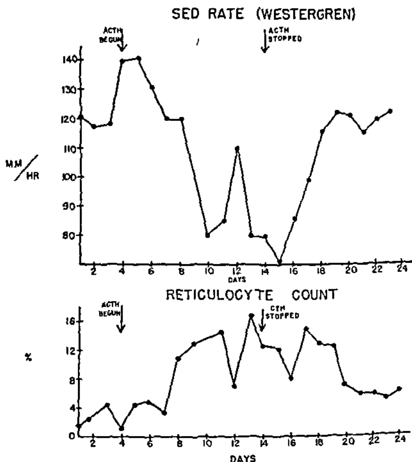
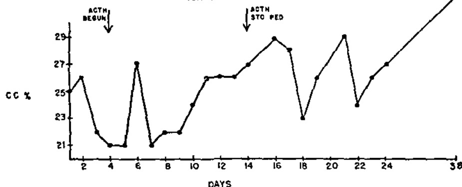


Fig 2

the period of administration, with the cessation of ACTH returned to and remained around 6,000 per cu mm The total eosinophile count which averaged only 15 cells per cu mm immediately prior to ACTH (Armour) was depressed during treatment to an average value of 5 cells per cu mm When ACTH was discontinued the eosinophiles promptly rose to and remained in the neighborhood of 50 per cu mm The elevated white blood count immediately prior to institution of ACTH and possibly the initially low eosinophile count may have been due in whole or in part to a subcutaneous abscess which developed at



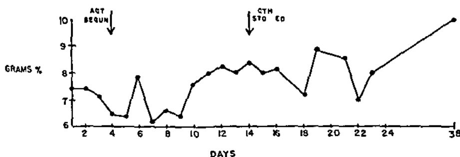


Fig 3

the site of an old hypodermic injection Thorn s belief that the low eosinophile count is due to bone marrow hypoplasia is not confirmed by the initial leukocytosis and reticulocytosis which this patient pre sented

The blood electrolytes including sodium potassium and chlorides from initial values which were slightly low returned toward normal These adjustments of the electrolytes were maintained during the 10 day post treatment follow up Serum calcium was not significantly changed

The low urinary excretion of sodium remained depressed during the first 6 days of ACTH but during the last 4 days of administra tion there was an escape with the daily sodium excretion being normal Then 24 hours after ACTH was discontinued sodium excretion again fell for 4 days before returning to high values Urine chloride excre tion behaved like sodium The urine potassium which was initially low at approximately 7 mEq daily rose by the second day of ACTH administration to 18 mEq per 24 hours The excretion of potassium then remained in the vicinity of 30 mEq per 24 hours throughout the

treatment period On the second day after ACTH was discontinued the potassium excretion rebounded to 9 mEq per 24 hours, remaining at approximately this level for 4 days before returning to excretion values of 25 mEq daily

The daily urinary excretion of total nitrogen and phosphorus



Fig 4

were not appreciably changed by ACTH Urine uric acid and 17 ketosteroid excretions were unequivocally enhanced by ACTH (Armour)

DR J S L BROWNE In connection with the treatment of lupus erythematosis, as reported, I want to show a case treated with testosterone in 1943, a young girl with typical lupus erythematosis She received 50 mgs of testosterone propionate a day Her fever did subside and she had a complete remission under this treatment It is of course impossible to exclude a spontaneous remission

The next year she came back with a relapse she was treated again with the same dose Her urinary corticoids which were very high were repressed but there was no effect upon her clinical course and she died

Here then we have a situation in which either a spontaneous



FIG 5

remission occurred or testosterone affected the disease The repression of the gluco corticoids would certainly have occurred in the first course of treatment as in the second You have a situation here where under the same treatment there were two quite different effects one a remission and the other no remission There was probably a repression of the gluco corticoids and repression of the adrenal in both instances

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DR WILLIAM S CLARK Our results with disseminated lupus erythematosus have been the same as reported, and these results need no further documentation However I think it would be worth while to show the slides that Dr Bauer spoke about, so that we can better understand the degree of reversibility in some of these diseases

The first photomicrograph (Fig 4) is the biopsy of the skin taken before ACTH therapy It shows pericapillary hemorrhages and infiltration with the various types of inflammatory cells particularly around the appendages

The second biopsy (Fig 5), taken 4 days later shows an almost completely normal skin, with some fibrosis

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Relief of Allergic Diseases by ACTH Therapy

Theron G Randolph and John P Rollins

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL CHICAGO

A clinical study of the effects of adrenocorticotrophic hormone (ACTH, Armour) in allergic states was suggested by the action of this hormone on circulating eosinophils[1] and the relationship of pituitary adrenal activity to the immune reaction [3 4]

Preliminary observations outlined in this paper indicate that the administration of ACTH materially relieves certain acute and chronic allergic symptoms in addition to affording protection to the allergic individual from the experimental exposure to allergens for which he has a specific sensitivity

Three patients with intractable perennial bronchial asthma of 7 to 15 years duration who had failed to respond adequately in spite of the avoidance of incriminated food allergens the avoidance and specific therapy with incriminated inhalant allergens and who required the oft repeated administration of epinephrine aminophyllin or anti histaminic medications were selected for ACTH therapy Two male patients aged respectively 43 and 76 years had no clinical or x ray evidence of emphysema or other apparent complications of bronchial asthma The third patient a female aged 50 subject to incapacitating asthma for the past decade had both clinical and x ray evidence of moderately advanced pulmonary emphysema The patients were hospitalized 48–96 hours prior to starting treatment with ACTH During this preliminary period only aminophyllin was administered as necessary for relief of severe asthma

Serial vital capacity and expiratory rate determinations were recorded prior to during and following ACTH therapy The vital capacity was determined as the result of averaging three readings The technique for determining the expiratory rate was modified after that originally described by Hamburger[5] it consists in measuring the time required to exhale an arbitrarily selected volume of air the amount chosen being in relation to the patient s vital capacity and measured in terms of the cubic centimeters of air expired per second

Twenty five milligrams of ACTH was injected intramuscularly every 6 hours for 2 days in the first and third patient and for 3 days in the second patient, making a total dosage of 225 0 and 325 0 mgm respectively

Clinical improvement as judged by the severity of symptoms was

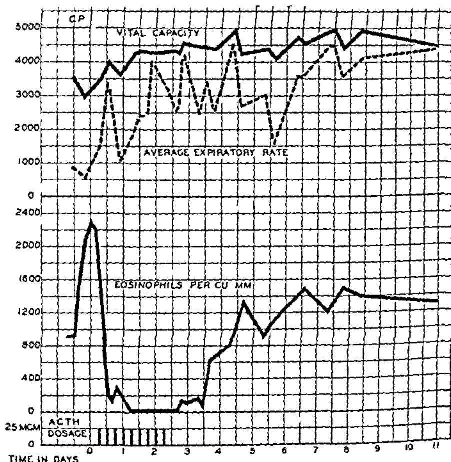


Fig 1

first noted in each instance between 4 and 5 hours after the initial dose of 25 0 mgm (Fig 1), coincident with a marked reduction in the number of eosinophils in the peripheral blood and bronchial secretions and an increase in the vital capacity and expiratory rate as shown in Figs 1 2 and 3 Maximum relief of symptoms in the second and older individual was more delayed It is interesting that the symptomatic relief obtained in the third patient with accompanying emphysema was as striking as observed in the first and second patients although the objective evidence of increased pulmonary ventilation

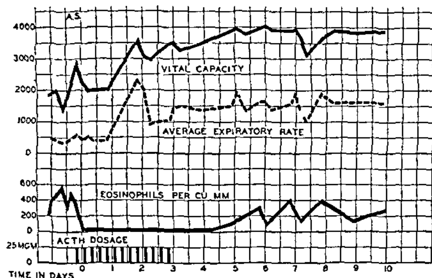


FIG 2

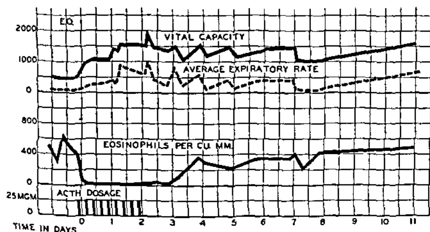


FIG 3

was not as apparent (Fig 3) A fourth patient a male aged 55 and subject to intermittent asthma since the age of 10 years and having a marked degree of emphysema was treated with ACTH on a similar schedule but failed to obtain more than 50% improvement of his respiratory symptoms He also required the use of epinephrine for symptomatic relief beginning 5 days after cessation of therapy

With the exception of this instance the other three patients re

mained markedly improved for a period of 21 days following the cessation of treatment. Although mild residual symptoms of asthma persisted in each, these were not of sufficient severity to require medication and aside from the administration of aminophyllin during the first 24 hours of therapy in the older individual no other medications were required. In each instance there was a gradual recurrence of asthma during the fourth week which required the use of symptomatic measures for relief.

At this point the first three patients were rehospitalized having asthma of the former severity, and given a second identical course of ACTH; this in turn was followed by an almost identical improvement.

Four patients with acute ragweed hay fever were hospitalized for a period of one week between August 31 and September 11, 1949. They were placed in standard hospital rooms with open windows and observed for 2 days prior to starting therapy. During this interim the daily incidence of coughing, sniffling and sneezing was recorded. During the entire period of observation the ragweed pollen count remained elevated (over 300 pollen grains per cubic yard of air per day) and hospitalized control untreated patients continued to have severe hay fever.

Each patient noticed an increased ability to breathe through the nose, partial relief of the rhinorrhea and the toxic or constitutional symptoms of hay fever during the first hour after the initial intramuscular injection of 25.0 mgm. This dose was continued at 6 hour intervals for 24 hours in one case, 48 hours in two and 56 hours in the fourth patient, as shown in Table 1.

Table 1

CLINICAL RESPONSE IN PATIENTS WITH RAGWEED HAY FEVER TREATED WITH ACTH

Cases	Age	Sex	*Pre Treatment*		*Treatment with ACTH*		*Post Treatment*				
			48 Hrs Before	*24 Hrs Before*	*Total Dosage in Mgm*	*Duration of Dosage in Hrs*	*1st 24 Hours*	*2nd 24 Hours*	*3rd 24 Hours*	*4th to 6th Day*	*10th Day*
M A	38	F	++++*	++++	125.0	24	+	0	0	0	0
H D	43	F	++	++	225.0	48	++	+	0	0	0
B H	38	F	++++	++++	225.0	48	++	+	0	0	0
D S	41	F	++++	+++	250.0	54	+++	++	0	0	+

+ = 1–50 coughs, sniffles or sneezes per 24 hours
++ = 50–150
+++ = 150–400
++++ = Over 400

Fig 4 illustrates the response in the first patient receiving a total dosage of only 125 0 mgm ACTH The incidence of coughing sniffling and sneezing as recorded by nurses in constant attendance changed from 640 times during the 24 hours prior to therapy to 30 times during the period of therapy and was virtually nil thereafter She had no further hay fever during the ragweed season She also had complete relief of her perennial nasal allergy and allergic head

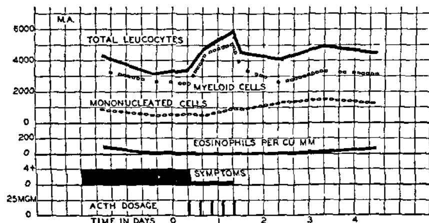


Fig 4

aches in spite of the daily ingestion of known food allergens for the following 3 months It should be stated however that this patient received estrogen therapy for several months prior to the administration of ACTH for relief of menopausal symptoms following x ray castration It was discontinued during ACTH therapy but resumed 10 days thereafter

Of the other patients receiving from 225 0 to 250 0 mgm total dosage two continued without troublesome hay fever for the remainder of the ragweed pollenating season one had a recurrence of mild hay fever the fourth day after the cessation of therapy Recurrent symptoms in this instance however represented a material improvement as compared with her level of symptoms prior to treatment or with those occurring in previous pollen seasons

The response in these patients was not related to previous ragweed therapy The first and third patients had never received specific treatment the remaining two had been treated pre seasonally although the fourth patient had not received her ragweed treatment for a month prior to the administration of ACTH

A male aged 31 and subject to atopic dermatitis since childhood had obtained complete relief of eczema for a period of a year as a

result of the avoidance of wheat Progressive flexural dermatitis had been present for a month prior to treatment with ACTH as a result of the inclusion of wheat in his diet One week *prior to starting ACTH* therapy this patient was placed on a wheat free diet, this was followed by the subsidence of pruritus and progressive healing of the lesions On the fifth day of wheat avoidance and 2 days prior to starting ACTH therapy an individual food test[8] with wheat was performed This test was associated with the variations in the blood findings illustrated in the first portion of Fig 5 and a recurrence of pruritus and erythema of the affected skin sites beginning 10 hours afterwards Wheat was continued in the diet for the subsequent 10 days

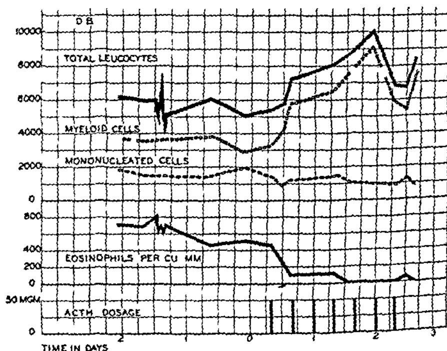


Fig 5

ACTH treatment at a level of 50 0 mgm every 8 hours was started 2 days after the experimental ingestion of wheat at a time when the dermatitis was in an acute oozing phase A total of 350 0 mgm ACTH was administered over a period of 50 hours He first noticed diminished pruritus 2 hours after the initial injection Progressive improvement of the dermatitis with objective evidence of rapid healing continued throughout the period of therapy and for 5 days thereafter During the following week he experienced a gradual recurrence of his dermatitis, reaching a greater degree of severity than ever previously observed

Another male patient aged 6 with a history of atopic dermatitis of the face anterior neck and flexural folds of the extremities since infancy, responded with approximately 75% relief as a result of allergic management He was known to be highly sensitive to corn in that its ingestion was invariably followed by an intense exacerbation of his dermatitis The deliberate feeding of corn for a preliminary period prior to starting ACTH therapy was followed by an acute exacerbation of his skin lesions Rapid improvement of the dermatitis as manifested by cessation of pruritus and progressive clearing of the erythema occurred coincident with a course of ACTH consisting of 16 6 mgm every 8 hours for the first day 25 0 mgm every 8 hours for the second day and every 6 hours for the third day resulting in a total dosage of 225 0 mgm in spite of the continued ingestion of corn products during the treatment period With the avoidance of corn following ACTH therapy this degree of improvement was maintained for a period of 10 days but then reverted to a greater degree of involvement than existed prior to starting these observations

One female aged 38 and subject to gastro intestinal allergy for many years was known to be violently sensitive to wheat developing acute abdominal cramps and diarrhea each time wheat was ingested Although previously controlled for several years as a result of the avoidance of incriminated food allergens she had developed an unexplained recurrence of her former symptoms 3 weeks prior to hospitalization for ACTH therapy She was treated with 25 0 mgm ACTH intramuscularly every 6 hours for a period of 80 hours receiving a total dosage of 325 0 mgm

Prior to therapy, as illustrated in Fig 6 she was having between 4 and 6 explosive diarrheic stools daily she continued at this level during the first and second days of treatment but beginning immediately thereafter she had no further evidence of colitis or other allergic symptoms Twenty four hours after the cessation of ACTH treatment she was fed experimentally a large serving of whole wheat gruel and although she anticipated an acute reaction she failed to show any evidence of a clinical response She then remained on a general diet including wheat and other food allergens several times per day for a period of 12 days without evidence of colitis or other symptoms gaining 10 pounds in weight Her abdominal cramps and diarrhea then recurred but were controlled for another week by the avoidance of wheat

Each of the first three asthmatics were also known to be clinically sensitive to several major foods In each instance individual food tests[6,7] performed immediately prior to starting therapy with ACTH

were associated with a sharp accentuation of asthma These deliberate feeding tests were repeated during or immediately after the cessation of ACTH treatment in each instance there was either a transient accentuation of symptoms or complete tolerance of the food in question

In addition to the localized manifestations of the allergic process as

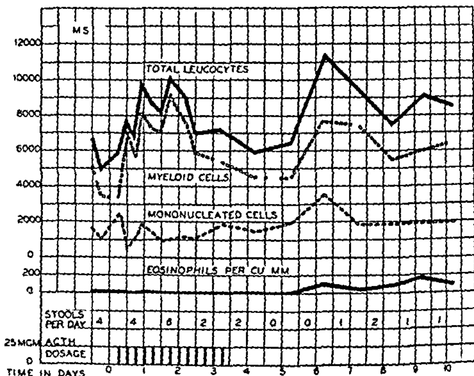


Fig 6

heretofore described many of these patients also complained of constitutional symptoms known to be associated with chronic allergic disease These have been described under the terms of allergic toxemia[8] or the fatigue syndrome of allergic origin [9] It is of interest to note that these symptoms of malaise, weakness ease of fatigue myalgia headache depression and dulled mental acuity were the first to be relieved following ACTH therapy in the proper dosage

The ability of adrenocorticotrophic hormone (ACTH) to change the clinical course of various allergic syndromes including bronchial asthma allergic rhinitis atopic dermatitis gastro-intestinal allergy and the fatigue syndrome of allergic origin as well as the ability to reduce or eliminate temporarily the clinical response following exposure to known inhalant or food allergens in specifically sensitized indi

viduals suggests that the basic mechanism of allergic disease is closely related to the function of the pituitary adrenal system

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DISCUSSION

DR THERON G RANDOLPH Another patient (see Fig 7) was chosen for ACTH therapy because she was the most violently pork sensitive patient in my practice The inhalation of cooking pork would give her intense headaches rhinitis and an acute gastro intestinal reaction

She responded to a very minimal dose and had relief of symptoms after 33 mgs of ACTH Twenty eight hours later she was fed a large dose of pork and although she had a blood respon e she did not have any adverse symptom response

We have since given ACTH to 3 pork sensitive patients chosen because of that factor and they have tolerated pork afterwards whereas

prior to that the ingestion of pork experimentally was associated with violent explosive allergic reactions

VOICE I would like to leave some objective evidence for the diagnosis of allergic colitis, and also I would like to know how Drs Randolph and Rollins eliminated the psychic effects of what has become a profoundly ritualistic psychotherapeutic experiment

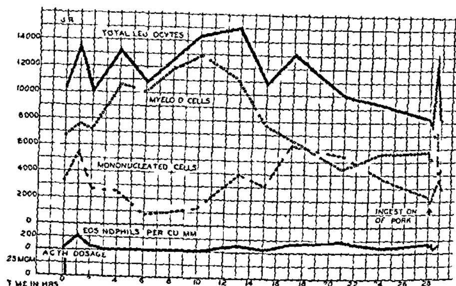


FIG 7

DR THERON G RANDOLPH The evidence for colitis in this case, of allergic origin was the fact that with the avoidance of wheat the colitis cleared up The experimental ingestion of wheat at repeated times caused a recurrence of the colitis The inadvertent ingestion of wheat accidentally at 4 different times gave the patient a sufficient g i reaction to cause hospitalization

It is impossible to rule out completely psychosomatic diseases, in view of the latitude the psychosomatists have taken

DR JEROME W CONN I would like to report two observations in two different individuals which vary somewhat from the usual responses One a boy, developed a giant urticaria from food sensitivity One injection of 25 mgs of ACTH essentially relieved it—and contrary to what we have heard, it returned again in 6 hours was again relieved in 2 hours with another 25 mgs

The other case was a young girl who was receiving ACTH daily On the sixth day of ACTH she developed hypersensitivity at the sites of the ACTH injections ACTH was nevertheless continued On the

day after the first sensitivity occurred she "blew up" with sensitivity at every prior site of ACTH injection

DR PETER H FORSHAM Two remarks about sensitivity Out of about 1 200 injections of 10–25 mgs of ACTH in various patients we have had two anaphylactoid reactions wherein the patient collapsed in about 10 minutes and was brought back very easily with adrenalin One patient was on pituitary extract therapy for years previous to injection which might have induced sensitivity

Then there was a child with Still s disease showing magnificent recovery with immediate fall in fever on ACTH but after 4 days the fever went up again and giant hives arose ACTH was stopped and the hives disappeared With 5 mgs of ACTH given 3 days later the hives reappeared

In giving patients repeated courses of ACTH it has been our experience in a number of such cases that the effect of an equivalent dose of ACTH was less marked on subsequent occasions than it had been during the first course Such findings might be interpreted as due to the formation of anti bodies to the relatively crude preparation of ACTH administered Caution must be exercised in the use of this interpretation because of (1) the variability of the potency of different batches of ACTH and (2) the changes in the state of the adrenal cortices of the patient treated by repeated courses of ACTH However when all this is taken into account there still remain some cases in whom the decreasing activity of a given daily dose of ACTH can not be explained by any of the above Preliminary observations in such a case show the presence of ACTH neutralizing antibodies Antigen anti body interaction is apparently markedly curtailed by ACTH We have found less resistance to the hormone with continued administration as opposed to a more frequent finding of such a resistance when the course of treatment has been interrupted for a matter of one to two weeks It may be that the very action of ACTH in reducing antigen anti body interaction accounts for the paucity of data suggesting anti body formation

Dr Bayles *mentioned that the gamma globulins did not* vary in rheumatoid arthritics given ACTH It is worth mentioning that in 4 cases of disseminated lupus we found an elevated gamma globulin which was markedly depressed by ACTH administration In Fig 8 are shown some interesting results obtained by Dr John Vaughn of the Peter Bent Brigham Hospital There is a profound fall of gamma globulins when ACTH becomes effective with a definite rebound after stopping it There is constant remarkable inverse relationship of the complement titer to the gamma globulin concentration in all of these cases

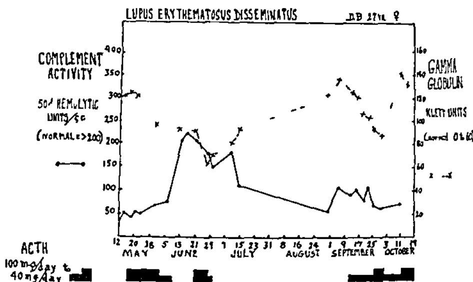


Fig 8

DR. EDGAR GORDON: Study of several patients with allergic states has revealed a complete lack of eosinophile response to administration of adrenalin followed by an extremely large response to 50 or 75 mg. of ACTH with the usual changes in output of 17 ketosteroids and 11 oxysteroids and accompanied by a dramatic clinical response. One of these patients was a case of urticaria and angioneurotic edema without any demonstrable, specific allergen sensitivities and a second case was severe intractable asthma with Loeffler's syndrome.

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Studies on the Effect of ACTH on Eosinophilia and Bronchial Asthma

Bram Rose

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This preliminary report is concerned with observations on the effect of ACTH in 2 cases of marked eosinophilia and 6 cases of bronchial asthma the latter of which comprise the first in a series of investigations on hypersensitivity

Following the demonstration by Thorn et al [1] that ACTH lowers the blood eosinophiles in individuals with intact adrenals and because of the relation of this cell to allergic states an opportunity to study the effect of ACTH on high eosinophilia was taken advantage of when a case of Loeffler s syndrome, and one of tropical eosinophilia were ad mitted to the Royal Victoria Hospital Montreal Th(fir t case a man of 44 had been admitted several times previously when the di agnosis was established Fig 1 shows two chest x rays taken in Sep tember and October 1947 which demonstrate the typical shifting

Table 1

EFFECT OF THE ADMINISTRATION OF ACTH TO A PATIENT WITH LOEFFLER S SYNDROME

D te and P oc du	T m	T t l W B C	P lym ph Total	%	E ph l T t l	%	% Cha g	Lymph yte T t l	%	M T t l	%	B T tal	%
17 10 47	p m	7 100	2 710	38	865	40 4	0	1 40	4 5	497	7 0	4	0 6
	4 15 p m	15 900	9 840	(1 9	179	13 5	−33	2 110	13 3	795	5 0	48	0 3
	9 p m	10 520	13 170	8 8	164	1 6	−94 4	1 6)0	10 6	684	4 3	45	0 3
	11 45	10 8(0	8 9 0	8	54	0 5	−)8 2	1 300	1 0	530	4 9		0 2
18 10 47	p m 11 15	11 590	7 010	60 6	680	5 9		596	2_ 4	1 2_9	10 6	58	0 5
_0 10 47	a.m 1 15	7 290	2 360	32 4	1,540	21 ?		2 480	34 0	940	12 9	43	0 6
_ 10 47	noon 15	7 050			1 105	0 9							
24 10 47	p m 1 15	5 480	5 6	9 6	1 146	0 9		2 6 0	47 8	)81	17 9	60	1 1
3 11 47	noo 12 oon	8 920	4 040	45 3	850	9 5		3 _90	36 9	669	7 5	71	0 8
10 11 47	1 15 oon	8 608	4 550	52 8	699	8 1		790	3 4	6 0	7 ?	26	0 3



Fig 1 a Chest x ray of the patient with Loeffler s syndrome taken on September 28 1947

pulmonary infiltrations Since it is known that these infiltrated areas consist in the main of eosinophiles it was felt that serial chest x rays during ACTH administration might reveal changes providing these eosinophiles were related to those in the peripheral blood Previous haemograms had shown the total W B C at 22 000 with eosinophiles varying from 3 to 44%

On October 17 1947 control studies showed a total W B C of 7 000 of which 2 140 or 18% were eosinophiles using Randolph s

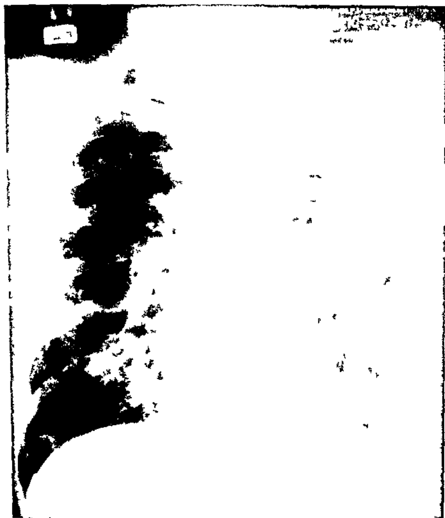


Fig 1 b Chest x ray of the same patient as shown in Fig 1 a taken on October 10 1947 The shifting areas of infiltration are shown

method [2] ACTH was administered in 50 mgm doses at 2 3 30 5 and 6 30 p m It was lot 32 D the total dose of which was equivalent to 140 mgm of Armour Standard As shown in Table 1 and Fig 2 there was a marked reduction of eosinophiles equal to 98% by the tenth hour after the initial dose Other alterations such as the initial leucocytosis and moderate lymphopenia are apparent Serial haemograms were made during the subsequent week and at intervals of 6 months since that time Of particular interest therefore is the fact

that the circulating eosinophiles have never returned to their pre ACTH level since that time to our knowledge, and this is now a period of over 2 years

Examples of the chest x rays taken at 1 and 4 hours after the first dose of ACTH are shown in Fig 3 There appeared to be a slight in

EFFECT OF ACTH ON EOSINOPHILES IN A CASE OF LOEFFLER S SYNDROME

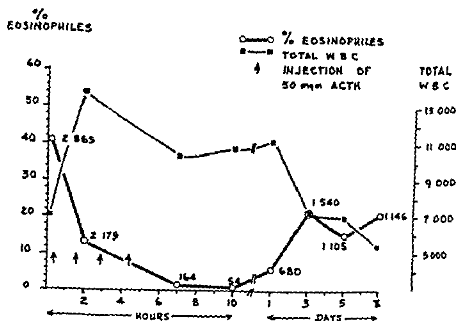


FIG 2 Showing the changes in the total white count and eosinophiles following ACTH therapy in the case of Loeffler s syndrome

crease in the density of the infiltrations on the 4 hour plate although this may be difficult to identify in the accompanying reproductions However 3 days later the lungs had markedly cleared, and have since appeared normal as demonstrated by periodic x rays Furthermore there has been no recurrence of symptoms Following ACTH the depression and cough disappeared and the patient gained steadily in weight Nevertheless the marked remission of symptoms here could not be ascribed with certainty to the effect of ACTH because of the well known tendency in this disease to spontaneous remission

The case of tropical eosinophilia, a young Indian student aged 21 had been in hospital for some weeks in December 1947 and January

1948 complaining of sore throat cough malaise and loss of weight before the diagnosis was established A complete investigation including the search for parasites was unfruitful excepting for the typical changes in chest x rays and marked eosinophilia The total W B C had been 46 630 of which 39 130 or 83 9% were eosinophiles The typical widespread miliary like infiltrations in the lungs are shown in Fig 4 ACTH was administered on February 21 1948 in two injections of 120 mgm each (lot 37 KE) at 10 15 a m and 3 p m The total dose was equal to 120 mgm Armour Standard

In Table 2 and Fig 5 it will be seen that the eosinophiles were reduced from 39 400 to 25 700 by the twelfth hour which represents a 37% reduction Serial x rays taken at intervals of 1 hour throughout the day of ACTH administration showed no alteration nor did subsequent plates taken at 2 day intervals for the next 2 weeks The haemograms repeated at 1 and 2 weeks post treatment were essentially unaltered At this time the patient was started on weekly injections of mapharsen Within 3–4 weeks there was complete remission of symptoms which would substantiate the diagnosis of tropical eosinophilia It is probable that the duration of ACTH administration was inadequate but this will require further investigation

Table 2

EFFECT OF THE ADMINISTRATION OF ACTH TO A PATIENT WITH TROPICAL EOSINOPHILIA

Date and Period	Time	Total W B C	Polymorphs Total	%	Eosinophiles Total	%	% Change	Lymphocytes Total	%	Mono Total	%	Baso Total	%
21 2 48	10 a m	46 630	980	6 4	39 130	83 9	0	3 160	6 8	1 [illegible]00	2.5	150	0 3
120 mgm ACTH	10 15 a m												
	1 p m	61 670	8 640	14 0	49 400	80 ?	+ 6	? [illegible]90	3	1 3 0	1	25	0 04
	4 p m	51 900	9 6 0	18 5	38 [illegible]00	73 6	−3	2 330	4 4	1 750	3 3	0	0
120 mgm ACTH	4 10 p m												
	8 15 p m	50,[illegible]00	1 [illegible]300	4 5	3? 400	64 5	−18	3 450	6 8	1 960	3 9	107	0 2
	11 15 p m	47 000	13 300	8 ?	25 700	54 6	−35	4 530	9 6	2 890	6 1	170	0 3
6 2 48		57 050			47 350	83							
5 3 48		38 250			26 775	70							

The observations on these two patients were made with a view to studying blood histamine levels associated with changes in eosinophiles as well We had previously observed that no correlation existed between blood histamine and fluctuations of eosinophiles Blood histamine determinations taken at the time the blood eosinophiles were evaluated in these two patients showed only minor fluctuations Of greater significance was the fact that the histamine values were all within the range of normal despite the marked eosinophilia and subsequent reduction in these cells These studies carried out with Drs Herbert and de Fries have since been reported [3,4]



FIG 3 a Chest x ray on the patient with Loeffler s syndrome on the day of ACTH administration 1 hour after initial dose of ACTH

The investigations on the effect of ACTH on asthma and other forms of hypersensitivity are being conducted in association with Drs J A P Pare K Pump and R L Stanford It had been previously demonstrated that the adrenal cortex bears a direct relation to the metabolism of histamine, and its specific enzyme histaminase in that the tissue and blood histamine is markedly increased and the mechanism for the destruction of histamine is impaired following removal of the adrenal in the rat [6 7 8] These alterations could be fully



FIG 3 b Chest x ray on the same patient as shown in Fig 3 a taken on the day of ACTH administration 4 hours after the initial dose of ACTH It will be seen that this 4 hour plate was taken at a time when there was a considerable reduction in the total eosinophile count and that there was some increase in the density of the areas of infiltration

restored only by administration of cortin and therefore presumably compounds like E or F, but not by desoxycorticosterone [8] In addition p gnancy which is associated with an increase of urinary glyco corticoids[9] as well as plasma histaminase[10] often causes a remission of symptoms in the asthmatic [11] We had previously shown that compared

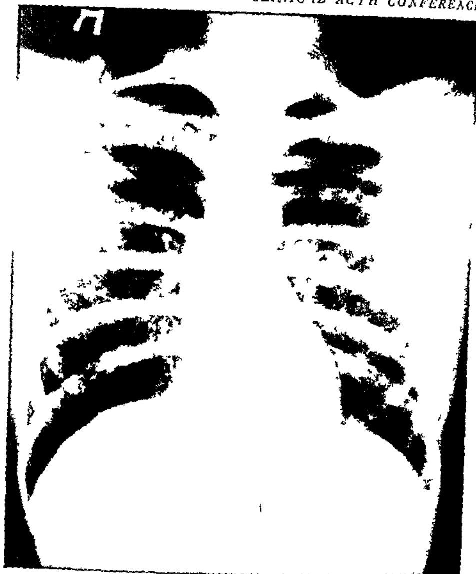


FIG 4 Chest x ray plate on the patient with tropical eosinophilia showing the typical miliary densities scattered throughout both lung fields

to the normal pregnant woman the level of plasma histaminase is impaired in the asthmatic who fails to go into remission during pregnancy[1] Recent studies on human tissues reveal that the histamine content of lung skin or mucous membranes from antra are much higher in the case of allergic patients as compared to those from normals[1] With these facts in mind as well as the knowledge that Loeffler s syndrome is usually complicated by asthma, the studies on ACTH were started

Since it is difficult under the best of conditions to assess the effect of any therapeutic agent on asthma it was felt desirable to study patients who had been followed for many years, whose asthma was severe and where daily medication of either adrenalin aminophyllin or other agents was a necessity

Each patient of whom there are now 6 had complete medical and

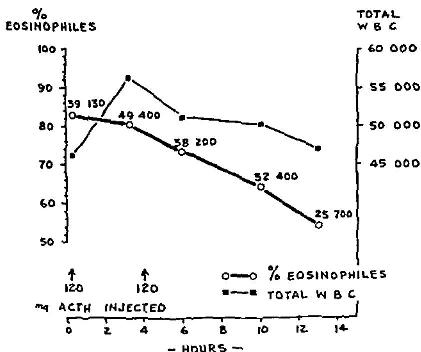


Fig 5

allergic investigations prior to admission All were admitted to the metabolic ward of the Royal Victoria Hospital where they were observed for a period of 9 days prior to treatment During the entire period of hospitalization the patients were kept on a fixed caloric and electrolyte intake The urinary output was measured and balance studies on nitrogen sodium chloride and potassium made In addition urinary excretion of 17 ketosteroids glycogenic corticoids histamine and histidine were measured They were allowed non specific medication such as adrenalin or aminophyllin as required

crease in pulmonary function in that the pre exposure M B C was now 116 l/min whereas it had been 86 l/min before treatment In addition whereas it took 10 inhalations to produce severe symptoms within 5 minutes before treatment 20 inhalations after 20 minutes of trying produced only minor changes in the respiratory function and there were no symptoms clinically

2 Thickened nasal and antral mucous membranes with polypoid formation shrank somewhat under the influence of ACTH but we have not as yet observed complete regression

3 Positive skin tests of the direct type were not altered by the administration of ACTH in the 3 patients where they were positive before treatment

4 The longest remission so far observed was 1 month after which it took 2 weeks for the symptoms to return to their former state

5 The eosinophiles were reduced to zero by 24 hours in 5 patients but this required 60 hours in the sixth patient

6 In all there was a marked increase in the urine histidine output the levels of which were similar to those seen in pregnancy (see Table 3)

Table 3

INFLUENCE OF ACTH ON URINE HISTIDINE IN AN ASTHMATIC

Patient I D			
	Days		mg/24 hrs
Control	1		97 5
	2		97 5
	3		68 1
	4		68 1
	5		111 0
	6		lost
	7		141 4
ACTH	1	100 mgm	236 1
	2	100 mgm	251 4
	3	100 mgm	254 0
	4	75 mgm	352 8
	5	75 mgm	373 0
	6	75 mgm	362 0
	7	50 mgm	213 2
	8	50 mgm	193 1
	9	25 mgm	298 7
Post ACTH	1		129 8

7 All of these cases showed excess histamine in the urine before treatment In 5 there was a marked reduction in the urine histamine output whereas in a sixth it was increased (see Table 4)

Table 4

INFLUENCE OF ACTH ON URINE HISTAMINE IN AN ASTHMATIC

Patient J T D			
Days			*per 24 hrs*
Control		1	2800
		2	2800
		3	4000
		4	4000
		5	900
		6	900
		7	2400
ACTH	100 mgm	1	25
	100 mgm	2	400
	100 mgm	3	300
	75 mgm	4	13
	75 mgm	5	23
	25 mgm	6	30
Post ACTH		1	9 3
		2	13 9

8 The urinary 17 ketosteroids were increased in 5 patients but failed to rise in the sixth

9 It is of interest that the failure of 17 ketosteroids to increase, and the delay in urine histamine and blood eosinophiles to decrease occurred in the same patient

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The Use of Adrenocorticotrophic Hormone in Chronic Liver Disease (Three Cases)

Lewis W Bluemle Jr Victor M Sborov Joseph Stokes Jr Paul Gyorgy and John R Neefe

ARMY HEPATIC AND METABOLIC CENTER VALLEY FORGE GENERAL HOSPITAL PHOENIXVILLE PA AND SCHOOL OF MEDICINE UNIVERSITY OF PENNSYLVANIA PHILADELPHIA

All cases following ACTH (Armour) therapy showed a characteristic drop in eosinophiles a negative nitrogen balance and a slightly or markedly increased uric acid creatinine ratio (except for one case whose ratio was not determined)

Case 1

J F male 37 years This veteran of 4 years military service in the South Pacific and a 10 year history of alcoholism developed deep jaundice in 1946 several months after discharge from the Service Following massive subcutaneous hemorrhages and irrationality bordering on coma he slowly improved over 3½ months Further symptoms appeared late in 1948 jaundice in April 1949 and coma in May 1949 with Cheyne Stokes respiration and fever ranging close to 102 He had continued to consume large amounts of alcohol until late April 1949 He was admitted to Valley Forge General Hospital May 2 1949 The liver was firm extending 12 cm below the right costal margin The spleen extended 7 cm below the left costal margin There were showers of spider nevi over the face neck and shoulders hypoplasia of the genitalia and moderate bilateral gynecomastia Rather rapid recovery from coma occurred possibly resulting from aureomycin 2 grams daily by parenteral injection following which jaundice gradually disappeared and the liver function tests returned toward normal ACTH was given during this recovery period primarily for the purpose of obtaining information concerning its harmlessness in such a severe case of portal cirrhosis Just prior to administration of ACTH the liver was palpable 7 cms below the right costal margin and the spleen palpable 7 cms below the left costal margin

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DISCUSSION

There was no discussion on this paper

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After 4 days of ACTH therapy (250 mgm) the liver size was unchanged and the spleen was palpable 8 cms below the left costal margin Immediately after completion of 7 days of ACTH therapy (500 mgm), the liver was felt 5 cms below the right costal margin and the spleen 4 cms below the left costal margin Throughout hospitalization there was a gradual reduction in the number of spider nevi and a decrease in gynecomastia, along with gradual increase in size of genitalia There was no perceptible acceleration of these changes during ACTH therapy A biopsy was taken within 2 weeks of onset of ACTH therapy and again 1 week after its cessation ACTH 500 mgm , was given over a period of 9 days There was a possible acceleration of recovery at this time The first biopsy indicated advanced fibrosis with fatty infiltration The second biopsy showed no change in the amount of fibrosis but apparently some decrease in the amount of fatty infiltration The effect of ACTH in this case was therefore equivocal but certainly not harmful

Case 2

R G , male, 42 years This sergeant with a strong alcoholic history began to have symptoms late in 1947 of nausea and anorexia, and gradually lost weight His diet at this time was poor In November, 1948 he noted onset of weakness in his legs exertional dyspnea, and continued weight loss In December 1948 on examination he had a large, firm, nodular, slightly tender liver, extending to the iliac crest He was admitted to the Valley Forge General Hospital in April 1949 The liver had apparently remained practically stationary and there were no spider nevi nor jaundice The spleen was not palpable Thymol turbidity was 3 4 units, and thymol flocculation 2+ The only important abnormal liver function test was a bromsulfalein retention of 9% At the time ACTH was started he was unable to walk up a short flight of stairs without complete exhaustion A biopsy was performed on May 12 1949 and again on August 11, one week after ACTH therapy which consisted of 500 mgm over a period of 9 days A striking improvement in appetite, activity, and sense of well being occurred by the fifth day of ACTH therapy His activity rapidly increased so that by 9 days after the stopping of ACTH he played of his own accord a full round of golf His weight preceding therapy was 130 lbs at the end of therapy 137 lbs and 42 days after therapy 148 lbs There was no drop of weight immediately after ACTH but rather a continuous slow rise which started at the initiation of therapy and remained unbroken up to 42 days following treatment His liver was palpable 10 cms below the right costal margin when ACTH therapy was initiated Upon completion of the 7 day course (500 mgm ACTH), it extended 7 cms below the right costal margin and 18 days

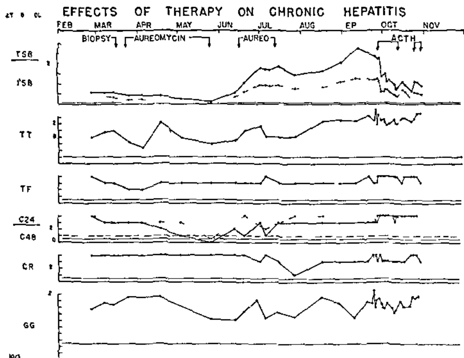


Fig 1

later it was palpable only 3 cms below the right costal margin The spleen was never palpable The biopsy on May 12 1949 showed severe portal fibrosis The biopsy one week after ACTH on August 11 1949 showed a striking decrease in the amount of fibrosis Regeneration of normal appearing liver tissue also had occurred The patient has remained in continued improvement up to the present time He was discharged from the hospital October 19 1949 completely asymptomatic He is now doing military duty He is to be readmitted May 1 1950 for followup evaluation The effect of ACTH in this case because of its severity and chronicity was quite as striking as that seen in rheumatoid arthritis following therapy with ACTH

Case 3

J T female 19 years Apparently an attack of viral hepatitis continued up to the present as a chronic viral hepatitis At onset minimal constitutional symptoms were greatly aggravated by physical activity The liver and spleen remained slightly enlarged but not tender A biopsy of the liver in March 1949 revealed some periportal fibrosis and considerable infiltration of mononuclear cells both intralobular

and extralobular Her progress following first two courses of aureomycin and then more recently a course of ACTH, 920 mgm over 13 days (80 mgm daily for 6½ days and 60 mgm daily for 6½ days) are shown in Fig 1 A moderate amount of ascites and edema of the face not previously detectable developed during the second week of treatment with ACTH and was associated with malaise and anorexia Following cessation of ACTH a spontaneous diuresis occurred with disappearance of ascites and facial edema Starting with ACTH therapy there has been a striking reduction of total serum bilirubin from 28 mgm % to 8 mgm to 11 mgm %, which has persisted and which has been followed by a greatly increased appetite and sense of well being Although not quite as striking an improvement as in Case 2 the results in this patient J F because of her chronic history over 18 months strongly suggest a favorable response to ACTH therapy Graphic chart for this patient is attached (Fig 1)

Two cases of viral hepatitis have been treated with ACTH as early as possible in the acute stage without evidence of improvement which could be attributable to such treatment However in the acute infectious hepatic disorders as opposed to chronic disorders a large series of cases with suitable controls would be required before any evidence for or against the value of ACTH could be obtained

DISCUSSION

DR WALTER BAUER The first patient with ulcerative colitis that I discussed this morning did have abnormal liver function tests The bromsulfalein test showed 17% retention of the dye and an alkaline phosphatase of 13 4 Bodansky units During the course of ACTH treatment the bromsulfalein test fell to 6% and the alkaline phosphatase to 2 4 units

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The Effect of ACTH on Patients with Pulmonary Tuberculosis*

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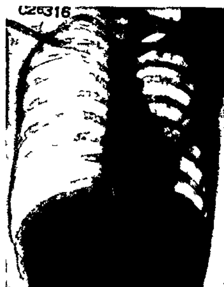
Two colored males ages 29 (C B) and 22 (F W) years with disseminated infiltrative tuberculous lesions of the left upper lobes were subjects for this study They had been observed at Hines Hospital for 6 and 8 weeks respectively prior to the control period of this study The patients were maintained on a diet of constant composition with regard to calories protein purines sodium potassium calcium and phosphorus The following determinations were made at frequent intervals diurnal temperature variation physical findings sedimentation rate sputum examination complete blood count blood uric acid sugar sodium potassium chloride inorganic phosphorus carbon dioxide combining power nonprotein nitrogen and serum protein fractionation The urinary excretion of nitrogen creatinine uric acid chlorides phosphates calcium inorganic phosphorus sodium potassium and 17 ketosteroids was followed Urine collections were pooled in 3 day periods and preserved in a refrigerator with thymol Serial films of the chest (Fig 1) and carbohydrate tolerance tests were taken at weekly intervals ACTH administration (100 mg daily) was begun after 3 control 3 day metabolic periods had been completed The dosage of ACTH was reduced to 75 mg /day after 3 days and returned to 100 mg daily after one week on the lower dosage An intake of 100 mg daily was then maintained continuously for the subsequent 5 weeks The following changes occurred during ACTH administration

The diurnal fever largely disappeared 24–48 hours after ACTH administration was instituted there was a marked increase in appetite and sense of wellbeing One patient became euphoric after 3 weeks

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F W Before ACTH



F W After 4 weeks on ACTH



C B Before ACTH



C B After 4 Weeks on ACTH

Fig 1

on ACTH Coughing largely ceased in both patients and the daily volume of sputum was reduced to half the previous amount The physical findings suggested a reduction in pulmonary consolidation The roentgenograms showed an increase in pulmonary translucency during the third week of therapy Areas of translucency resembling evacuated abscesses appear in one patient s roentgenograms (Fig 1)

The changes in the roentgenograms of the other patient were less striking but indicated that similar changes were occurring The sedimentation rate declined after 3-5 weeks of ACTH Both patients developed a leucocytosis during the second week of therapy A lymphopenia and eosinopenia developed Both systolic and diastolic blood pressure increased after 3 to 4 weeks on ACTH The body weight increased somewhat during the first 2 weeks of ACTH and thereafter declined During ACTH administration there was an increase in CO_2 combining power and a slight decrease in the concentration of serum potassium The serum inorganic phosphorus value fell and the alkaline serum phosphatase of one patient (C B) rose significantly The serum phosphatase of the other patient remained relatively constant There was a prompt and marked increase in 17 ketosteroid excretion in both patients The fasting blood sugar level rose and the carbohydrate tolerance declined as ACTH administration was continued There was an increase in the urinary excretion of nitrogen uric acid potassium phosphorus and chlorides during ACTH administration Sodium excretion first decreased and then increased Urinary calcium excretion was somewhat increased by ACTH administration ACTH administration was associated with an increased plasma albumin and a decreased gamma globulin and fibrinogen The a/g ratio increased Changes occurring in the other fractions were irregular The sputum remained positive for tubercle bacilli throughout the study The laboratory data on both patients were so similar that only a part of it is presented in the following illustrations

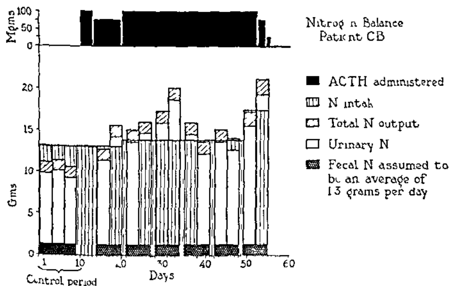


FIG 2

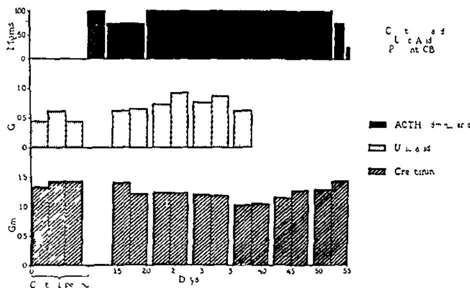

100
50
0
1.0
0.5
0
1.5
1.0
0.5
0
15
20
45
50
55
ACTH
Gm

Fig 3

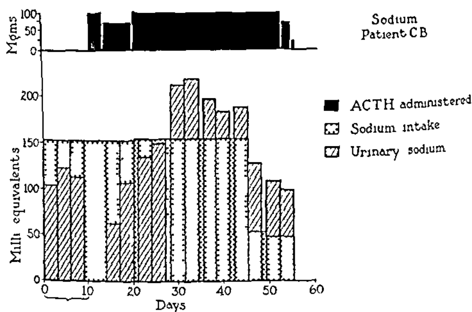

Sodium
Patient CB
ACTH administered
Sodium intake
Urinary sodium
Mgms
100
50
0
200
150
100
50
0
Milli equivalents
0
10
20
30
40
50
60
Days

Fig 4

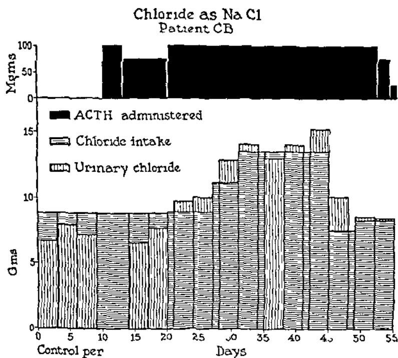

Chloride as Na Cl
Patient CB
100
50
0
Mgms
ACTH administered
Chloride intake
Urinary chloride
15
10
5
0
Gms
0 5 10 15 20 25 30 35 40 45 50 55
Control per
Days

Fig 5

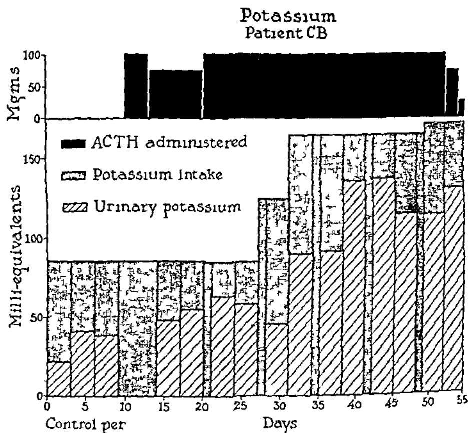

Potassium
Patient CB
Mgms
100
50
0
ACTH administered
Potassium intake
Urinary potassium
Milli-equivalents
150
100
50
0
0
5
10
15
20
25
30
35
40
45
50
55
Control per
Days

FIG 6

FIG 7

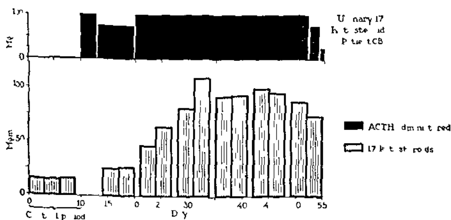


FIG 8

Blood Nitrogenous Constituents
Patient CB

ACTH administered
Uric acid
Total protein
Non protein nitrogen

Mgms 100 50 0
Mgms 10 0
Gm / 10 0
Mgm 40 20 0
0 10 20 30 40 50 60
Control per Days

Fig 9

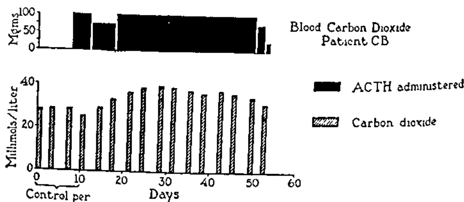


Fig 10

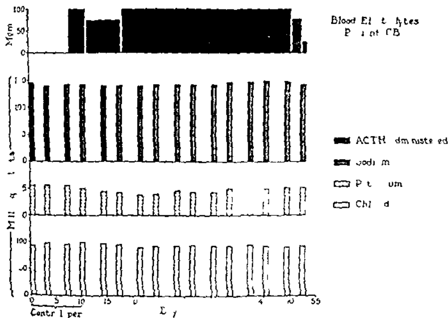

Mgm
100
50
0
ACTH
0
5
10
15
55
Contr l per

Fig 11

100
Mgms
50
0
8 9
8 19
9 0
Dates
160
140
120
100
80
60
Mgm
30
60
120
180
Minutes
9 1
8 9
8 15
8 4
Patient CB
ACTH administered
Glucose tolerance
Fasting blood sugar
150
100
Mgm
1
4
8
11
15
18
22
29
1
5
8
12
15
19
August
September

Fig 12

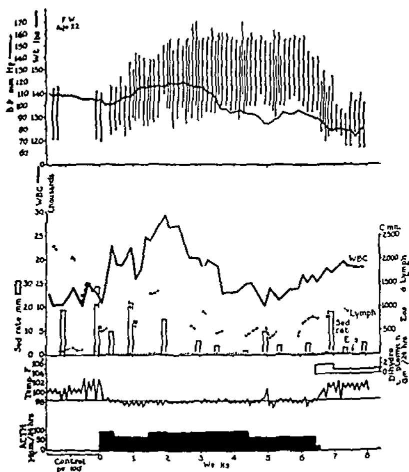


Fig 13

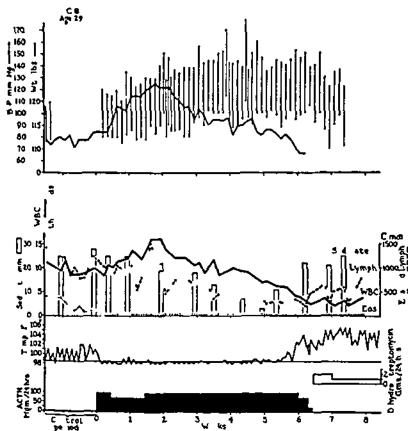


FIG 14

Electrophoretic Measurements of Plasma Proteins (Veronal buffer pH 86)

Patient FW

Date	ACTH adm st ed mg/day	Tot l p t n gms %	Album n %	Album n gms %	Globulins α 1 %	α 1 gms %	α 2 %	α 2 gms %	β %	β gms %	γ %	γ gms %	Fibri ogen %	Fibri ogen gms %	A/G ratio
8 8 49	C t l	6 72	34 92	2.34	8.82	0 58	17 10	1.15	9 69	0 65	16 24	1.09	13.25	0 89	0 67
9															
	100														
11															
12															
15	75	6 65	41 30	2 75	7 80	0 52	12 65	0 84	13 86	0 92	16 02	1.06	8.38	0 56	0 82
18															
19															
25		5 86	43 25	2 3	9 06	0 3	11 98	0.70	12.21	0 72	14 17	0.83	9 36	0 55	0 91
	100														
9 12		6.62	47 20	3 12	8 32	0 55	15 83	1.11	8.01	0 53	12 63	0 84	8 01	0 53	1.05
15															
16															
	75														
22															
23	25														
24															
	None														
26		5 91	35 39	2 09	10 10	0 60	14 62	0 86	11 68	0 69	13.57	0.80	14.62	0.86	0 71

FIG 15

DISCUSSION

DR ALLAN KENYON I would like to ask Dr Freeman whether he feels the lesion has advanced, or not

DR PETER H FORSHAM I would like to show one slide which refers to some work done by Dr C B Favour and his associates at the Peter Bent Brigham Hospital Guinea pigs (Fig 16) sensitized to tuberculin showed disappearance of the tuberculin skin reaction while on ACTH Following discontinuance of ACTH it reappeared Suitable controls all showed a good tuberculin reaction Complete correlation was obtained by the use of the lympho lysis test in which lymphocytes from tuberculin sensitized guinea pigs are lysed by adding tuberculin in vitro The lymphocytes were lysed before and after ACTH, but not during ACTH administration

Thus, under the action of ACTH the hypersensitivity phase of the reaction to tuberculin was abolished Dr Favour has since extended these observations to man

The dangers of such a reaction in the treatment of human tuberculosis remains to be evaluated

Treatment	Animal Number	PPD before ACTH	PPD after 15 days ACTH	PPD 10 days following ACTH
ACTH	1			
	3			
	5			
	7			
SALINE	2			
	4			
	6			Died
	8		Died	

ACTH

Days 1 5 10 15 20 25 30

Effect of ACTH on Tuberculin Skin Reaction in Guinea Pigs Appropriate controls all negative

FIG 16

DR SMITH FREEMAN In one patient there was a definite spread of tuberculosis during the period of ACTH administration In the other patient extension of the pulmonary lesion was questionable Sputum remained positive in both patients throughout the study and after discontinuation of ACTH

44

The Use of ACTH in Poliomyelitis*

Lewis L Coriell and Lois Murphy

MUNICIPAL HOSPITAL OF CAMDEN N J AND THE CHILDREN S HOSPITAL OF PHILADELPHIA

Alan C Siegel

HARVARD MEDICAL SCHOOL BOSTON

Joseph Stokes Jr

THE CHILDREN S HOSPITAL OF PHILADELPHIA AND UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE PHILADELPHIA

Charles D Cook

HARVARD MEDICAL SCHOOL BOSTON

Certain data about poliomyelitis suggest an unusual host parasite relationship Among these are (1) the very low incidence (less than 1 in 100) of manifest disease among those infected (2) the familial incidence constitutional factors and hormone imbalance theories which have been advanced to explain susceptibility, (3) excessive fatigue and chilling or exhaustion during the incubation period is frequently followed by severe paralysis and (4) the greater incidence of infection in pregnant women as compared to non pregnant women All these observations suggest that susceptibility or resistance to poliomyelitis involves non specific defensive mechanisms and indirectly that the host response is more important than the virulence of the virus in determining the course of infection Rapid mobilization of bodily defensive mechanisms may limit the spread of infection in the usual subclinical case whereas a slower response as a result of constitutional factors or exhaustion may permit infection to spread In deed we do not know whether or not poliomyelitis precipitates "alarm reaction ACTH has been observed to produce this effect It occurred to us that this mechanism to act naturally might be at fault in those people who contract paralytic poliomyelitis

For these reasons the therapeutic use of ACTH in early polio-

Aided by a grant from The National Foundation for Infantile Paralysis

myelitis seemed worthy of a trial Ideally one should test this theory by giving the ACTH during the first few days of the incubation period and it is fully realized that its use after the disease is manifest may prove nothing However with the encouragement of Dr Mote of the Armour Laboratories a cautious therapeutic trial was made and this led to the study reported here It was believed that the following questions might be answered (1) Is the alarm reaction evoked by poliomyelitis? (2) What is the physiologic action of ACTH in poliomyelitis? (3) Does ACTH modify the course of poliomyelitis when administered early in the course of the disease?

Single doses of varying amounts of ACTH were given to a number of poliomyelitis patients at the Camden Municipal Hospital No deleterious effects were observed so two patients were placed on a daily maintenance dose of 50 mgm for 4 days In both patients the temperature returned to normal within 12 hours and the progression of paralysis ceased The good results in these two patients suggested that a definitive trial with a significant number of patients should be run without waiting for further animal experiments Since only sporadic cases were occurring in southern New Jersey the study was moved to the Children s Medical Center at Boston where an extensive epidemic was in progress

STUDY PLAN

To be admitted to the study patients were required to present at least 4 of the 7 criteria set forth by the National Foundation for Infantile Paralysis namely, history fever stiff neck stiff back not less than 10 or more than 500 cells in the CSF elevated CSF protein and demonstrable muscle weakness In addition we required that patients must have been ill less than 5 days and have fever of 100 5 or more A total of 70 patients were studied 35 receiving ACTH and 35 as controls

Patients admitted to the study were given ACTH or a placebo as determined by random selection through drawing balls of two colors from a container All medication was given intramuscularly at 6 hour intervals for 4 or 5 days The identity of the medication was unknown to the nursing and medical staffs who cared for and evaluated the patients The dosage schedule of ACTH is shown in Table 1

For the first part of the study crystalline penicillin was used as the placebo This was later changed to physiological saline when it was pointed out by Dr Forsham that the eosinophile count might be altered in persons hypersensitive to penicillin

The criteria for activity of the drug and adequacy of dosage were obtained by (1) eosinophile counts done initially at 4 hours then

Table 1

DOSAGE SCHEDULE OF ACTH IN MGM./DAY DIVIDED INTO 4 EQUAL DOSES AND ADMINISTERED INTRAMUSCULARLY

Wt kg	Day of Therapy			
	1	2(R2)	3	4
−20	40	40	20	20
20–40	60	60	40	20
40–60	80	80	60	40
60+	120	100	80	60

daily during therapy, and for 8 days after discontinuing therapy (2) excretion of 17 ketosteroids, and (3) by blood chemistry, Na K, and fasting blood sugar when indicated

The first 18 patients (R on Fig 1) received ACTH as shown above

The next 17 patients (R2 on Fig 1) were maintained at the dosage shown for the second day of therapy in Table 1 for a period of 5 days

The observations of clinical improvement were made by the medical staff and tabulated daily by Dr Siegel on prepared forms Only objective criteria were used These included (1) the temperature response (2) progression or remission of paralysis, (3) the muscle spasm and tenderness, and (4) later orthopedic followup for recovery from residual paralysis

Stools from 40 patients were frozen at 20°C for future use and paired acute and convalescent sera from 14 patients were stored

RESULTS

The total number of cases in the study appears to be adequate to give a definite and clear cut answer to the questions posed As shown in Table 2, the median day of hospitalization was almost identical

Table 2

DISTRIBUTION OF CASES

	Control	ACTH
Total number	35	35
Median day of hospital	2 6	2 5
Nonparalytic	13	12
Paralytic	22	23
% Paralyzed	63	66
Deaths	0	1

for the two groups as was the distribution of paralytic and non paralytic cases

Practically every patient had a low eosinophile count on admission In the control group the eosinophile count rose gradually to normal levels on the second hospital day with a continued rise or rebound to higher levels on the fifth to seventh day The group receiving ACTH had a sharp drop in eosinophiles 4 hours after the first dose and the count remained down until the drug was discontinued when a more marked rebound occurred The average eosinophile count of each group is plotted in Fig 1 which also shows that the rebound of eosinophiles was delayed one day longer in the 17 patients who received ACTH for 5 days instead of 4 days The higher initial eosinophile count in the group which received ACTH is caused by

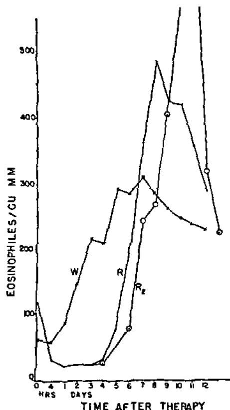


Fig 1 Eosinophile response in poliomyelitis W = Average count of 35 patients who received a placebo every 6 hours for 4 days R = Average count of 18 patients who received ACTH in decreasing doses every 6 hours for 4 days R_2 = Average count of 17 patients who received a constant dose of ACTH every 6 hours for 5 days

one patient who had an initial count of 2100/cu mm If this count is omitted both groups have an average initial count between 50 and 60/cu mm

Excretion of 17 ketosteroids was determined in 8 patients The first 24 hour urine was collected on the second day of ACTH therapy and the control specimen on the tenth hospital day, 5 or 6 days after therapy was discontinued The results shown in Table 3 are somewhat variable, but it seems clear that the control cases had no increased 17 ketosteroid excretion in the 2 specimens tested Those treated with ACTH did have higher levels in the first specimen as well as the second specimen in a few instances

Table 3

17 KETOSTEROID EXCRETION

Name	Age	Sex	Medication	mgm /24 hrs	
				2d Day	10th Day
E L	15	M	ACTH	16 1	4 87
P F	7	F	ACTH	2 20	0 34
B M	15	M	ACTH	14 3	6 55
W W	7	M	ACTH	1 72	1 61
H B	16	M	ACTH	32 6	13 81
G E	6	M	Control	1 08	1 06
E H	6	M	Control	1 01	0 55
R S	7	M	Control	2 05	1 0

We conclude from the eosinophile counts and 17 ketosteroid excretions that the dosage of ACTH was adequate to produce a physiologic effect

The course of the disease in individual patients was extremely variable and in some patients the use of ACTH seemed to have effected a dramatic termination of fever and paralysis In fact, after we had treated 7 patients in each group, it appeared that the 7 receiving ACTH were benefited Here we wish to stress the fallacy of drawing conclusions from a few cases for with increased numbers of patients it became quite clear that there was no detectable difference between the two groups Table 4 shows the distribution of cases on the basis of clinical type of poliomyelitis

In Table 5 it is obvious that the average days of fever in the control and treated groups was 5 6 and 5 7 days respectively, and the average days of fever after treatment was 2 9 and 2 8 days Paralysis progressed in the control group for 4 5 days from onset and for 2 4 days after

Table 4

NUMBER OF CASES OF VARIOUS CLINICAL TYPES

	Control	*ACTH*
Nonparalytic	13	12
Spinal s̄ Resp Inv	13	16
Spinal c Resp Inv	0	1
Bulbar s Resp Inv	8	4
Bulbar c̄ Resp Inv	1	2
Totals	35	35

Table 5

AVERAGE DAYS OF FEVER AND PARALYSIS PROGRESSION IN TREATED AND CONTROL GROUPS

	Fever				*Paralysis*			
	Total		*After Treatment*		*Total*		*After Treatment*	
	W1	*R2*	*W*	*R*	*W*	*R*	*W*	*R*
Nonparalytic	5 0	5 3	2 9	3 0	—	—	—	—
Spinal	5 7	5 7	2 8	3 1	5 4	4 8	2 7	2 9
Bulbar	6 2	6 0	3 0	2 3	3 7	3 9	2 2	1 6
Average	5 6	5 7	2 9	2 8	4 5	4 4	2 4	2 2

W1 —Control patients who received the placebo
R2—Treated patients who received ACTH

treatment was started and in the ACTH group the figures were 4 4 days from onset and 2 2 days after treatment

Frequent examination of patients by the orthopedic staff of the Children s Medical Center did not reveal any difference between treated and control patients in spasm, pain tenderness or the duration of the sensitive stage The long term follow up of these patients is being carried out

SUMMARY

The alarm reaction is mobilized in poliomyelitis as shown by the eosinophile response In these patients ACTH produced a physiological effect as evidenced by a further depression of eosinophils and by increased excretion of 17 ketosteroids There was no demonstrable effect in the treated as compared to the untreated group when eval

uated on the basis of (1) temperature response, (2) paralysis, (3) progression of paralysis, or (4) residual effects

Statistical analysis shows clearly that ACTH has no beneficial or obvious deleterious effect on the course of poliomyelitis when treatment is begun after onset of symptoms

DISCUSSION

There was no discussion on this paper

45

Effects of ACTH in Primary Atypical (Viral) Pneumonia and in Pneumococcal Pneumonia (Preliminary Report)

Maxwell Finland Edward H Kass and Sidney H Ingbar

THORNDIKE MEMORIAL LABORATORY SECOND AND FOURTH MEDICAL SERVICES (HARVARD) BOSTON CITY HOSPITAL AND HARVARD MEDICAL SCHOOL BOSTON

W'th the Te h l A s stance f

Cla e W'l o H l C Alpe t a d M ld d W Ba

Dr Mote's invitation to investigate the action of ACTH in certain acute infections was welcomed as an unusual opportunity to re investigate many aspects of infectious diseases that are poorly understood We wish to present here certain of the findings in 2 patients one of them may be termed a classical case of the so called viral or primary atypical pneumonia the other a case of pneumococcal pneumonia The former was of considerably more than average severity in a young adult the latter was of moderate severity in an adolescent Only those results which are related to the clinical response and the bacteriological and serological findings will be presented in any detail Some of the biochemical findings will only be alluded to briefly but details will be omitted at this time

The first patient (Fig 1) was a 28 year old housewife who was admitted with a history of fever headache muscle aching and a non productive cough of 3 days duration She had been treated with penicillin at home during these 3 days On entry she was prostrated acutely ill flushed feverish but mentally clear Temperature was 104 2° pulse 100 respirations 24 There were physical signs and x ray findings consistent with consolidation of most of the left lower lobe The white blood count was 3900 with 61% polys 37% lymphs and 2% monocytes The urine was negative Sputum was scanty mucoid and contained many mononuclears, occasional polys and few organisms Cultures of the sputum and throat cultures yielded *Streptococcus viridans*, *H influenzae* and *Neisseria flavus* Blood culture showed no growth The patient was given 100 000 units of penicillin every 4 hours for the next 3 days during which she continued to have tempera

ture rises to 104° falling only in response to the administration of aspirin There was an increase in pulmonary infiltration by x ray although the physical signs were not very striking at any time

On the fourth hospital day the patient was started on doses of 25 mg of ACTH (Armour) every 6 hours At the time of the first dose the temperature was 102° and pulse 96 The patient was flushed, very weak fatigued, anorexic coughing frequently and complaining of generalized aching and severe headache The total leucocyte count was 4900 with 54% polys 42% lymphs and no eosinophils

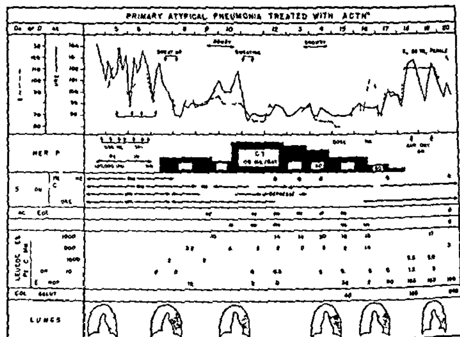


Fig 1

Within 6 hours after the first dose of ACTH (Armour) (no further *aspirin was given*) the temperature began to fall and within 18 hours was 98° During this time diaphoresis began and the patient exhibited a definite sense of well being Within 24 hours she was afebrile, free of muscular pains and headache and was beginning to eat but was still coughing rather severely and raising a good deal of mucoid sputum The signs in the chest were unchanged

On the second day of therapy malar flush and facial edema appeared and so on the third day the daily dose of ACTH (Armour) was dropped to 75 mg The temperature promptly rose to 101 8° and mild headache reappeared Meanwhile the patient s urine volume which had been much decreased during the preceding 2 days, rose

markedly and her weight dropped 5½ pounds within 24 hours The white blood count rose to 10 000 with 75% polys and 15% lymphs Eosinophils which had begun to appear increased in the course of 36 hours to 150

The patient was therefore given 50 mg of ACTH every 6 hours Within 12 hours she was again afebrile euphoric and feeling quite well She again became oliguric and regained 6 pounds of weight Her cough persisted although it was less severe than previously and the physical signs and x rays of her chest showed very slight if any clearing

The dose of ACTH was continued at 200 mg per dav for 2 davs but when marked facial edema malar flush and oliguria reappeared the do e was gradually decreased over a period of 6 days and then stopped During this period of withdrawal just as during the earlier period when this was attempted the patient was quite drowsy but otherwise felt quite well

The x rays of the chest showed slow but steady clearing The cough persisted but became progressively less severe The patient s white blood count rose steadily to 16 000 with slowly increasing eosinophil counts The urine volume likewise increased gradually the facial edema regressed but the feeling of well being persisted until the last 24 hours of therapy during which she received only a total of 25 mg At this time her temperature again rose to 100° and after all therapy was withdrawn it rose further to 102 8° Repeated sputum studies re vealed only *Streptococcus viridans* and rare polymorphonuclear cells

The patient now felt weak listless and was quite depressed She cried frequently and expressed morose apprehension about her ulti mate recovery Her cough was less severe than it had been and x rays of her lungs although showing considerable patchy infiltration gave evidence of progressive clearing

Because of the recurrence of fever and the rise in the white count to 24 200 she was given 1 gm of aureomycin intravenously every dav for the next 4 days The fever nevertheless recurred each day but the leucocyte count dropped sharply She is still weak (Oct 22) but is no longer depressed and she coughs rather frequently During the third week of her illness the patient first developed cold agglutinins and Strep MG agglutinins which increased steadily to a maximum titer of 1 640 and 1 160 respectively

While the patient was receiving 50 mg of ACTH (Armour) every 6 hours she developed glycosuria which persisted for 4 days and then cleared as the dose of ACTH was decreased The fasting blood sugar, previously normal was elevated to 139 on one of the days when gly cosuria was present The patient s hematocrit had dropped during ACTH administration from 40 to a low of 34 and within 48 hours

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On the fourth hospital day the patient was started on doses of 25 mg of ACTH (Armour) every 6 hours At the time of the first dose the temperature was 102° and pulse 96 The patient was flushed very weak fatigued, anorexic coughing frequently and complaining of generalized aching and severe headache The total leucocyte count was 4900 with 54% polys, 42% lymphs and no eosinophils

PRIMARY ATYPICAL PNEUMONIA TREATED WITH ACTH

Fig 1

Within 6 hours after the first dose of ACTH (Armour) (no further aspirin was given) the temperature began to fall and within 18 hours was 98° During this time diaphoresis began and the patient exhibited a definite sense of well being Within 24 hours she was afebrile, free of muscular pains and headache and was beginning to eat but was still coughing rather severely and raising a good deal of mucoid sputum The signs in the chest were unchanged

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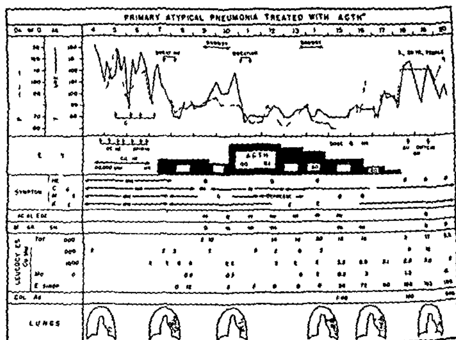


Fig 1

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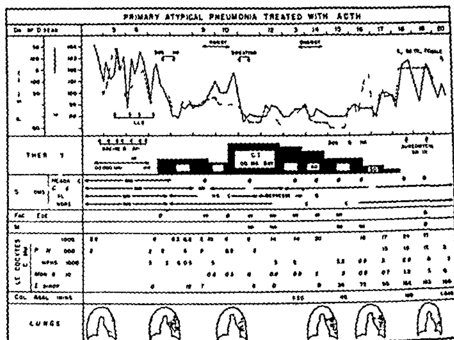


FIG 1

Within 6 hours after the first dose of ACTH (Armour) (no further aspirin was given) the temperature began to fall and within 18 hours was 98° During this time diaphoresis began and the patient exhibited a definite sense of well being Within 24 hours she was afebrile, free of muscular pains and headache and was beginning to eat but was still coughing rather severely and raising a good deal of mucoid sputum The signs in the chest were unchanged

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The dose of ACTH was continued at 200 mg per day for 2 days but when marked facial edema malar flush and oliguria reappeared the do e was gradually decreased over a period of 6 days and then stopped During this period of withdrawal just as during the earlier period when this was attempted the patient was quite drowsy but otherwise felt quite well

The x rays of the chest showed slow but steady clearing The cough persisted but became progressively less severe The patient s white blood count rose steadily to 16 000 with slowly increasing eosinophil counts The urine volume likewise increased gradually the facial edema regressed but the feeling of well being persisted until the last 24 hours of therapy during which she received only a total of 25 mg At this time her temperature again rose to 100 and after all therapy was withdrawn it rose further to 102 8° Repeated sputum studies re vealed only *Streptococcus viridans* and rare polymorphonuclear cells

The patient now felt weak listless and was quite depressed She cried frequently and expressed morose apprehension about her ulti mate recovery Her cough was less severe than it had been and x rays of her lungs although showing considerable patchy infiltration gave evidence of progressive clearing

Because of the recurrence of fever and the rise in the white count to 24 200 she was given 1 gm of aureomycin intravenously every day for the next 4 days The fever nevertheless recurred each day but the leucocyte count dropped sharply She is still weak (Oct 22) but is no longer depressed and she coughs rather frequently During the third week of her illness the patient first developed cold agglutinins and Strep MG agglutinins which increased steadily to a maximum titer of 1 640 and 1 160, respectively

While the patient was receiving 50 mg of ACTH (Armour) every 6 hours she developed glycosuria which persisted for 4 days and then cleared as the dose of ACTH was decreased The fasting blood sugar previously normal was elevated to 139 on one of the days when gly cosuria was present The patient s hematocrit had dropped during ACTH administration from 40 to a low of 34 and within 48 hours

ture rises to 104° falling only in response to the administration of aspirin There was an increase in pulmonary infiltration by x ray although the physical signs were not very striking at any time

On the fourth hospital day the patient was started on doses of 25 mg of ACTH (Armour) every 6 hours At the time of the first dose the temperature was 102° and pulse 96 The patient was flushed, very weak, fatigued, anorexic coughing frequently and complaining of generalized aching and severe headache The total leucocyte count was 4900 with 54% polys, 42% lymphs and no eosinophils

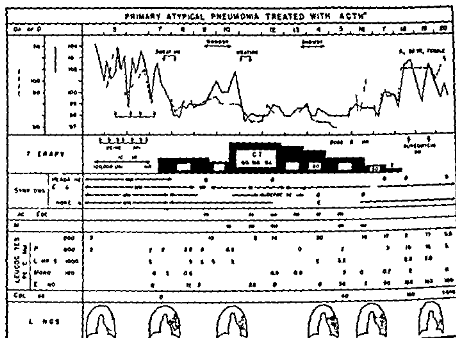


FIG 1

Within 6 hours after the first dose of ACTH (Armour) (no further aspirin was given) the temperature began to fall and within 18 hours was 98° During this time diaphoresis began and the patient exhibited a definite sense of well being Within 24 hours she was afebrile, free of muscular pains and headache and was beginning to eat but was still coughing rather severely and raising a good deal of mucoid sputum The signs in the chest were unchanged

On the second day of therapy malar flush and facial edema appeared and so on the third day the daily dose of ACTH (Armour) was dropped to 75 mg The temperature promptly rose to 101 8° and mild headache reappeared Meanwhile, the patient s urine volume which had been much decreased during the preceding 2 days rose

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after therapy was stopped, it rose again to 42 5 The eosinophil count gradually returned to normal during and after the period of withdrawal Of interest is the fact that herpes simplex appeared during the time when the dosage of ACTH was being reduced and the lesions persisted throughout the next week

This interesting case is not yet completed * It is apparent that ACTH did not hasten the resolution of the lesion but did bring about remarkable temporary remission in the clinical appearance and symptomatology of this patient

The case of pneumococcal pneumonia (Fig 2) was in a 16 year old schoolboy who entered the hospital 2½ hours after experiencing the sudden onset of severe left sided chest pain followed quite promptly by a shaking chill The patient had had an upper respiratory infection with a cough productive of mucoid sputum during the previous week and during the day prior to entry his cough had increased in severity and his sputum had become brownish When first seen he appeared acutely ill flushed and drowsy His temperature was 104, pulse 120 respirations 36 There were physical and x ray findings of a small area of consolidation in the left lower lobe The sputum was gray and tenacious and a smear and Neufeld test showed it to be loaded with type 8 pneumococci and polymorphonuclear leucocytes The white blood count was 16,500 with 88% polys The blood culture taken at this time showed no growth The urine was negative

The patient was observed without treatment for 8 hours During this time the temperature fluctuated from 101 4° to 104 2° and the pulse stayed at 120 At the end of this period the white blood count was 25 000 with 90% polys the hematocrit was 43 and there were no eosinophils

ACTH (Armour) was then started and administered intramuscularly every 6 hours Two doses of 25 mg were followed by 50 mg doses for 72 hours after which the daily dose was gradually diminished until the drug was withdrawn after 5 more days At the time of the second dose, the patient was still acutely ill his temperature was 103 6° white blood count 35 000 and there was no change in the physical signs in his chest Within the next 12 hours there was profuse diaphoresis the temperature dropped sharply to 98° the pulse fell to 80 and the respirations to 20 Sputum at this time became rusty, was still loaded with type 8 pneumococci they all appeared viable, with no evidence of phagocytosis The patient himself felt much improved began to eat had no more chest pain coughed only rarely

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* The patient was subsequently continued on oral doses of aureomycin 0 5 gm every 4 hours for 11 more days The fever returned slowly to normal By the time the patient was discharged there was still slight residual pneumonitis demonstrable by x ray and this cleared slowly

and had essentially no complaints However a blood culture taken at this time was positive for type 8 pneumococcus and the total white count was still 27,800

On the following day the chest was virtually clear, the white blood count was 18,000 with 96% polys the sputum was now scanty but still loaded with pneumococci and there was no evidence of phagocytosis in the smear A blood culture taken at this time which was 36

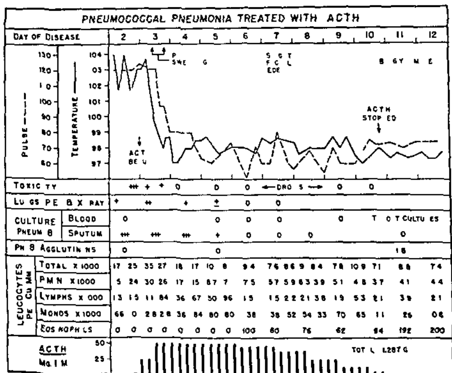


Fig 2

hours after the first dose of ACTH and 24 hours after the temperature had reached normal was again positive for type 8 pneumococci

Repeated blood cultures after this time were negative Sputum no longer being available throat cultures were done and these have failed to show pneumococci by the usual cultural methods although type 8 pneumococci were still found by mouse inoculation of the throat culture on the day after the ACTH was stopped (This is not shown in Fig 2) The patient has remained afebrile and free of symptoms His white blood counts have been normal since the third day of therapy and his eosinophils have gradually returned to normal

The outstanding features of this case are (1) the rapid deferves

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DR EDWARD KASS Certain further observations of note may be summarized briefly

1 The first patient showed a characteristic escape phenomenon while receiving 100 mgm per day, as evidenced by the appearance of eosinophils and the reversal of her water retention These occurred along with increasing temperature and increasing signs of toxicity

2 Herpes labialis appeared in patient No 1 during the period that therapy was being withdrawn

3 Both patients evidenced considerably slower pulse rates during the period of therapy than after therapy had ceased This relative bradycardia should be added to the list of possible toxic manifestations of administration of ACTH

4 The sedimentation rates of the first patient did not change significantly as a consequence of administration of ACTH although the second patient s sedimentation rate returned slowly to normal during the first 8 days of observation

DR SIDNEY H INGBAR Although metabolic studies on these two patients are not yet completed several aspects are worthy of note

1 The uric acid creatinine ratio has not correlated at all well with the dosage of the drug indeed there were marked variations in the daily output of uric acid and creatinine

2 Both patients developed transient glycosuria with diminished glutathione levels of 14 7 and 15 3 mgs of GSH respectively As the glycosuria decreased the glutathione rose in the first patient In the second patient there was glycosuria in the presence of normal glucose tolerance and of glutathione level in the blood of 15 mgs %

cence, (2) the appearance of bacteremia at the time of the induced crises and its persistence for a time while the patient was afebrile and symptom free, (3) the persistence of pneumococci in the sputum after the crisis, and (4) the development of specific antibodies at the usual time It is highly unlikely that this prompt clinical recovery, the rapid clearing of the toxemia and of the pulmonary consolidation in spite of the presence of bacteremia could have been to chance alone

It is obvious from these preliminary findings that considerably more studies will be needed before these effects can be interpreted

DISCUSSION

DR S C TAYLOR I just want to state that we had one case on which we were cutting down ACTH, who developed a virus pneumonia We had reduced ACTH to 30 mgs a day in 3 divided doses He began running a temperature up to 103° with chills and fever and aching, and developed an area of consolidation in his right upper lobe, clinically acting like virus pneumonia He did not respond to any of the antibiotics, and I assure you we tried them all We omitted ACTH for a week, and his temperature continued The consolidation remained in the upper lobe At Dr Mote s suggestion we then started ACTH again at 100 mgs a day After the second dose of 25 mgs the temperature promptly dropped to normal and remained normal We kept it up for 2 days and then reduced the dose, and his temperature remained normal and his consolidation cleared up

DR JOHN R MOTE Of course, since my previous training was in preventive medicine and epidemiology and bacteriology and a few things like that this particular phase of this meeting is particularly intriguing to me because I think you are getting a few clues for the first time to a rational understanding of epidemiology

I certainly think there are enough fundamental things that have been talked about here which require considerable work, and will give a newer and enlightened sense of infectious disease and epidemiology

DR JAMES J SMITH It is interesting that one of our patients with delirium tremens, who responded very well to the administration of ACTH, had concomitantly a very severe pneumonia, and the way in which he handled his pneumonia was remarkable He was up and about the ward We simply couldn t keep him down It was quite remarkable I don t want to give you the impression that we could not keep him down because he was disturbed He was not disturbed We couldn t keep him in bed because he felt so well

Table 1

Patient	Age	Clinical Diagnosis	ACTH Dosage		Duration of Drug Administration (Days)
			(mg day)	Total (mg)	
1	40	Rheum arth	60–15	1125	27
2	34	Rheum arth	100–40	300	6
3	19	Rheum arth	40	280	7
4	62	Rheum arth	60–25	4200	5
5	45	Rheum arth	40	240	6
6	42	Rheum arth	100–40	580	13
7	49	Rheum arth	75–40	315	7
8	43	Rheum arth	100–40	340	7
9	35	Dermatomyositis	100	1800	18
10	20	Regional ileitis	50–100	1400	15
11	36	Tox diff goitre	100	1700	17
12	42	Tox diff goitre	100	1700	17
13	24	Schizophrenia	200	2000	10
14	39	Schizophrenia	200	2000	10

The psychiatric studies consisted wherever possible of an evaluation of the premorbid personality and of frequent interviews by one of us during the course of treatment In some of the earlier cases striking changes in personality and behavior were evaluated on the basis of reports by medical and nursing personnel

EEG FINDINGS

Prior to ACTH therapy 6 patients had essentially normal records One patient had one normal and one slightly slow record Seven patients had basically slightly slow records characterized by occasional runs of low to medium voltage activity at a rate of 5–7 cycles per second

During the course of ACTH administration the records of 2 patients remained unchanged one which had been normal the other one which had been slightly slow The other 12 patients showed significant moderate to marked changes in their records usually after 3–5 days These changes consisted of

A Reduction in amplitude regularity and continuity of the basic alpha activity and slowing of the alpha activity in the most striking case from a rate of 12–13/second to one of 7–8/second

B The appearance of large amounts of slow activity (3–7/second) which occurred at random or in bursts and which was often increased in incidence or amplitude or both in response to overventilation

In one instance spike activity appeared in addition to slowing and

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Electroencephalographic and Neuropsychiatric Changes in Patients Treated with Adrenocorticotrophic Hormone (ACTH)*

Paul F A Hoefer and Gilbert H Glaser

PRESBYTERIAN HOSPITAL COLLEGE OF PHYSICIANS AND SURGEONS COLUMBIA UNIVERSITY AND DEPARTMENT OF RESEARCH PSYCHIATRY NEW YORK STATE PSYCHIATRIC INSTITUTE

During the period from May to October 1949, 14 patients treated with ACTH were observed by the authors at the Columbia Presbyterian Medical Center in New York City

The medical diagnoses were as follows

Rheumatoid arthritis	8 cases
Dermatomyositis	1 case
Regional ileitis	1 case
Toxic diffuse goitre	2 cases
Schizophrenia	2 cases

The patients received amounts of ACTH (Armour) varying from 20 mgm to 200 mgm per day for periods of 1 week to over 4 months

Table 1 is shown to indicate the patients age diagnosis, dosage and duration of drug administration

The present report deals with two phases of clinical and laboratory investigation electroencephalographic and neuropsychiatric changes observed in these patients

The electroencephalographic records (EEG s) were taken with Grass equipment (6 and 8 channels) Standard monopolar and bipolar records were obtained and in each observation a 5 minute period of hyperventilation was included One or two control records were obtained prior to the period of treatment During the period of drug administration records were taken every 4–7 days in most instances A fina record was obtained about one week after termination of treatment

* Supported in part by the Masonic Foundation for Medical Research and Human Welfare

Table 1

Patient	*Age*	*Clinical Diagnosis*	*ACTH Dosage* (mg/day)	*Total* (mg)	*Duration of Drug Administration* (Days)
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7	49	Rheum arth	75–40	515	7
8	43	Rheum arth	100–40	540	[illegible]
9	35	Dermatomyositis	100	1800	18
10	20	Regional ileitis	50–100	1400	15
11	56	Tox diff goitre	100	1700	17
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EEG FINDINGS

Prior to ACTH therapy 6 patients had essentially normal records. One patient had one normal and one slightly slow record. Seven patients had basically slightly slow records characterized by occasional runs of low to medium voltage activity at a rate of 5–7 cycles per second.

During the course of ACTH administration the records of 2 patients remained unchanged, one which had been normal, the other one which had been slightly slow. The other 12 patients showed significant moderate to marked changes in their records, usually after 3–5 days. These changes consisted of:

A. Reduction in amplitude, regularity and continuity of the basic alpha activity and slowing of the alpha activity, in the most striking case from a rate of 12–13/second to one of 7–8/second.

B. The appearance of large amounts of slow activity (3–7/second) which occurred at random or in bursts and which was often increased in incidence or amplitude or both in response to overventilation.

In one instance spike activity appeared in addition to slowing and

in another runs of rapid activity (15/second) were interspersed with the slow activity

Characteristic EEG changes in two cases are shown in Fig 1

The EEG abnormalities became gradually more marked during the course of therapy but reverted in most instances to the pre treatment level within one week after the discontinuation of the drug

NEUROPSYCHIATRIC CHANGES

In most cases alterations in mood, affective level and behavioral activity were noted

The patients with rheumatoid arthritis showed an increasing feeling of well being, alertness and some tension and irritability as the symptomatic effect of the drug on pain and movement appeared This occurred within the first 3 days Six of these patients remained mildly elated or euphoric as long as the effect of the drug lasted and reverted rapidly, within one or two days to their previous state after the drug was discontinued One patient became increasingly elated and showed a more marked euphoria and marked hyperactivity, talking incessantly Another patient after becoming moderately euphoric two or three days after the drug was started, showed in addition insomnia irritability pressure of speech and finally developed a full blown manic psychotic reaction with clear sensorium, which persisted unchanged for 10 days after discontinuation of the drug It subsided finally after 4 electroshock treatments This patient had been ill for 19 years Prior to her illness she had an active outgoing personality with marked emotional lability During the illness she became bitter resentful and depressed She attempted suicide 10 days before admission to the hospital (and before ACTH therapy was started) The EEG in this patient showed marked disorganization of alpha activity slow activity (4–7/second) and interspersed rapid activity (15/second) at the height of the psychotic reaction

The patient with dermatomyositis had had episodes described as hysterical' in the past and was regarded as emotionally unstable and maladjusted in her marital life Four days after ACTH was started she became lethargic incontinent of urine dysarthric with wandering ideation and had an unsteady gait There were no other positive findings on neurological examination This state cleared after a few days but during this time definite changes in the electroencephalogram appeared of the type noted previously Seventeen days after the drug was started she was noted to have rapidly gone into a stupor which lasted about 36 hours then clearing spontaneously There were no significant neurological findings at this time An electroencephalogram taken one day prior to the onset of the stupor had shown notable

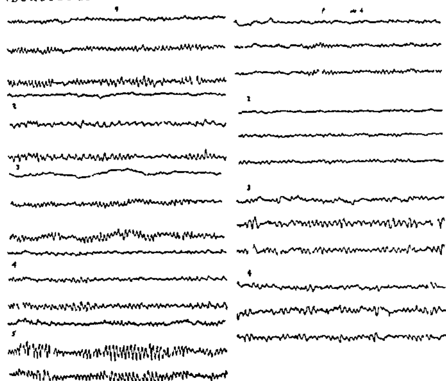


Fig 1 All leads shown right motor parietal and occipital

Patient 9 Dermatomyositis age 35

1 Pre ACTH record Normal 10 11/second (occasional rapid and spike 15/second also present)

2 ACTH 9 days 100 mg/day Alpha is disappearing and is being replaced by 4–5/second activity especially in parietal and occipital leads

3 ACTH 16 days 100 mg/day Record has improved with 10–11/second alpha appearing again

4 ACTH 18 days 100 mg/day Stupor present Alpha is less continuous more irregular and low voltage 5/second notched waves become dominant

5 Off ACTH 8 days Essentially normal record with dominant 10/second alpha throughout

Patient 1 Rheumatoid arthritis age 62

1 Pre ACTH record Mildly irregular with 10 12/second medium voltage activity throughout

2 ACTH 5 days 60 mg/day Alpha is lower in amplitude slower (8–9/second) less regular and less continuous Some 6–7/second activity is present

3 ACTH 14 days dose decreased to 15 mg/day on day of EEG Alpha rarely present Dominant medium and medium high voltage 6–7/second activity occurs throughout especially parietally

4 ACTH 21 days 20–25 mg/day The 6–7/second activity is somewhat less but still dominant

improvement, but the record during the stupor was again markedly abnormal with dominant 5/second low voltage activity throughout (see Fig 1 patient No 9) Eight days after the drug was discontinued the electroencephalogram had reverted to its pre drug pattern

The patient with regional ileitis though markedly schizoid, showed no significant personality changes while receiving ACTH One patient with toxic diffuse goitre became more tense and irritable during the period of drug administration, the other showed no significant changes The two patients with schizophrenia also showed no significant alterations in mental symptomatology however, further investigation on this group is being carried out

The electroencephalographic changes premorbid personality characteristics and mental changes are summarized in Table 2 A & B

The electroencephalographic changes cannot be explained on the basis of known mechanisms at the present time The following possibilities should be considered alterations in glucose metabolism changes in water metabolism, interference with the acetyl choline cycle, disturbance in potassium balance peculiar toxic' effect of the ACTH per se or through the excessive adrenal cortical steroids produced

Table 2A

Patient	Age	Clinical Diagnosis	Control EEG	EEG During Drug Administration	Premorbid Personality	Mental Changes
1	40	R A	1 Normal 9–11/sec 2 Sl slow 5–7/sec	Disorganized irreg low 3–5/sec esp during hyp	Some emotional instability	Mild euphoria
2	34	R A	Normal 10–12/sec	Irregular continuous alpha are 7/sec	Schizoid features	Moderate euphoria with verbal hyperactivity
3	19	R A	Normal 9–11/sec	Irreg 5–7/sec often in bursts	No significant features	Mild euphoria
4	[illegible]	R A	Normal 10–12/sec	Irreg 5–7/sec some 15/sec	No significant features	Mild euphoria
5	45	R A	Sl slow 6/sec	Irreg 4–6/sec incr with hyp	No significant features	Mild euphoria
6	[illegible]	R A	Normal 10–12/sec	Irreg alpha slowing Disorganized 5–7/sec 4–5/sec and 15/sec	Affective lability Suicidal attempt	Manic psychotic reaction
7	49	R A	Irreg small amt 5–7/sec	Increased 5–7/sec	No significant feature	Mild euphoria
8	43	R A	Irreg low 5/sec	No significant change	No significant features	Very mild euphoria

Table ?B

P t ent	Ige	Cl l D g	C t l FEC	FIC D g D ig Ilm ni l at	P morb d P lity	Ment l Ch g
9	35	D r n	No mal 10–11/sec (occ rap l a l p k 15/sec)	Alph abs nt l 4–5/sec esp par -occ and d g hyp	Em t llv u tabl ma tal mal lju tme t	St p st te
10	0	Reg l	I reg 5 7/sec	Furthe slow g to 4–5/sec esp d iring hyp	M rk dly schi d se al mm t nt	No s g fic t chang
11	36	Tox D G	Rare alpha d orga ed 4–6/sec D g hyp 10–1?/sec	Mo e diso g ized No lpha Slowing during hyp to 3/se	No s gn fic t fe ture	In reased tens on nd t b l t
1	4?	To D C	Alpha 12 13/sec occ 4 7/sec	Inc t 4–7 ec esp dur g hyp	N gn fic t f t es	N s gn f t ch ng
13	4	Sch z	I eg 5–7/sec R re alph	Further slow ng to 5 7/sec nd 3–4/sec oft in bursts	E o o all n t bl schi o d	No g fic t ch g
14	39	Sch z	Normal 10/sec	No g fic t chang	Em t onally u tabl sch o d	N g fic t ch g

With regard to the mental changes a similar situation exists particularly since a suggestive correlation with the electroencephalo graphic disturbances occurs in some cases The minor mental re actions could be regarded most probably as normal responses to the relief from chronic painful symptoms since these reactions primarily occur in the arthritics However since more severe reactions occur in arthritics and in other disease entities two other factors have to be considered (1) The occurrence of an organic mental reaction as mani fested by the stupor state of one case and correlated electroencephalo graphic changes, (2) a released psychotic reaction with exaggeration of premorbid personality trends as shown by the manic reaction in one patient Certainly both factors could be operating in any in dividual case These changes could not be correlated with drug dosage levels or alterations in blood sugar or electrolytes

This is a preliminary report and further studies are in progress in the hope of clarifying these electroencephalographic and mental changes occurring during ACTH administration

DISCUSSION

DR GEORGE W THORN Just this comment One sees abnormalities in personality at both ends of the picture that is the patient with Ad dison s disease often exhibits abnormalities in personality and as you

know, we have been able to show that one may correct the abnormally slowed electroencephalogram in Addison's disease with Compound E

All of us who have dealt with patients with Cushing s disease recognize the frequency with which abnormalities in personality exist Kepler often remarked on this point We have found fast rates to predominate in the electroencephalogram

DR HUDSON HOAGLAND The slowing of the electroencephalogram reported by Drs Hoefer and Glaser following prolonged massive doses with ACTH is especially interesting to me because it is contrary to

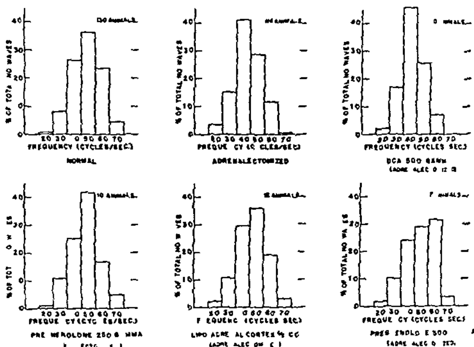


Fig 2

what one might expect in view of electroencephalogram slowing reported both by Thorn and his group and by Engle and collaborators in Addisonian patients Here hypoadrenalism produced a slowing while in the cases of Hoefer and Glaser excessive activity of the adrenal also slows brain wave frequencies Mr John R Bergen of our laboratory has just completed a study of the electrocorticogram in rats He finds that adrenalectomy shifts the entire spectrum to the slow side and that this shift is restored to normal by small doses of Δ 5 pregnenolone and by adrenal cortical extract but not by desoxycorticosterone Fig 2 shows his results The shift in the spectrum and the restoration are significant at the 1% level of confidence by chi square tests The

slowing of frequencies in adrenalectomy is also consistent with the findings of the investigators mentioned above in hypoadrenalism in man resulting from Addison s disease This would lead me to wonder if the slow wave production we have just seen in hyperadrenalism following massive and repeated doses of ACTH may not be due to secondary causes such as excessive shifts in water balance in the brain due to the prolonged and unusual action of repeated medication with ACTH

DR GREGORY PINCUS I would like to make one remark about EEG In adrenalectomized animals there is a marked slowing of the EEG rhythm and DOC does not restore this but in experiments Dr Hoagland and some of the men in our laboratory have been doing they found that Δ 5 pregnenolone restores it very well and so does adreno cortical extract We have not used compound E

As far as comments on schizophrenic patients are concerned I think we have *indicated that a proportion show interesting and definite re*sponses to stresses and ACTH At the Worcester State Hospital we have confined our attention to schizophrenic men only and cannot speak about adrenal responsivity in other psychoses It should be obvious from the data Dr Hoagland presented that an adequate series of cases is needed for a full understanding of adrenocortical function in the complex schizophrenic psychosis

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Pituitary-Adrenocortical Function in Patients with Severe Personality Disorders

Hudson Hoagland and Gregory Pincus

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY AND THE WORCESTER STATE HOSPITAL SHREWSBURY MASS

This paper presents a brief summary of the work of our group in the study of adrenal cortical function in ' mental' patients It is a survey of many published papers and of work now under way

Engaged in these studies in the past 6 years in addition to the writers have been Harry Freeman, Fred Elmadjian, Louise Romanoff William Malamud, Sidney Sands Enoch Calloway Justin Hope, Victor Schenker, Eliot Rodnick, Austin Berkeley, and some 20 technicians

The work has been aided by the Office of Naval Research, the U S Public Health Service the Williams Waterman Fund of the Research Corporation Armour and Company and the G D Searle Company

Specific citations are not included in this brief review

Chronic schizophrenic patients, not subjected to special stresses, give evidence of adrenal cortical secretion differing little from normal controls Thus we have found that the 24 hour excretion of 17 keto steroids potassium and uric acid in 40 patients and 40 controls fasted over night is not different although a significantly smaller excretion of neutral reducing lipids was observed in the patient group The patients also excrete significantly more sodium and more urine but water intake was not adequately controlled and these last results are hard to evaluate

We have studied adrenal cortical function in approximately 100 psychotic patients and 200 control subjects divided according to age in a variety of stressful tests These tests have been exposures to heat and high humidity, exposure to cold, the fatiguing operation of an airplane type pursuit meter at sea level and at reduced oxygen tensions, the stress of ingesting large doses of sugar, psychological tests such as interviews, and a specially designed frustration test Urine and

blood samples were taken before each test which lasts an hour, 15 minutes after the test and again at 2 hours and 15 minutes post test The urinary samples were analyzed for 17 ketosteroids reducing lipids, sodium, potassium uric acid and inorganic phosphate Lymphocyte counts were made on the blood samples and also eosinophile counts in many of the tests

Not all the subjects have been through all of our tests and studied by all our indices, but our findings have been evaluated statistically and may be summarized by saying that the patient group (schizophrenics hospitalized an average of 2½ years) failed markedly to enhance adrenal cortical output with stress as compared to the control group This is true especially for purely physiological stresses as well as for psychological stresses Fig 1 shows typical differences in responses

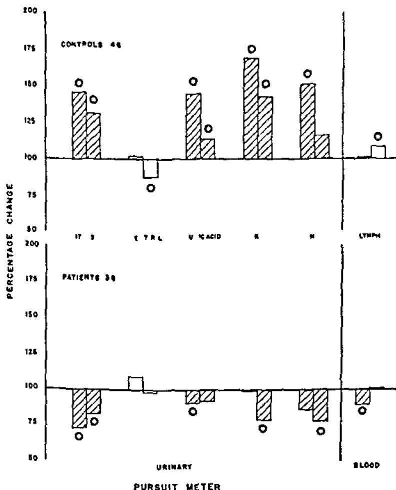
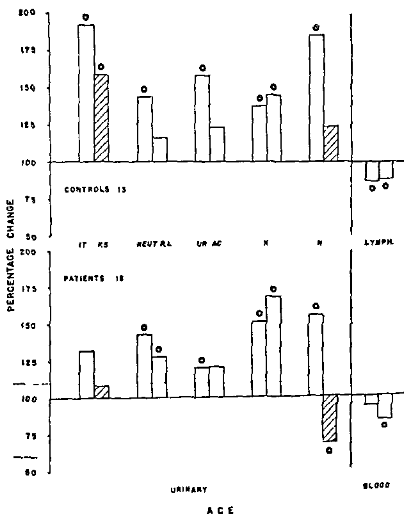


Fig 1

to an hour of operation of a pursuit meter by 46 controls and 36 patients The first rectangle of each pair represents per cent changes from pretest levels at 15 minutes post test and the second rectangle shows changes at 2¼ hours post test Circles above the rectangles represent changes from resting levels at better than the 5% level of confidence and cross hatchings indicate differences between patients and controls at this same level of confidence Control urine and blood samples were collected over the first 2 hours after rising and the post test samples were late morning samples We have demonstrated a diurnal rhythm of adrenal secretion which is maximal after rising and which falls during the day If the stress does not enhance adrenal output the values of the urinary variables should fall below the resting



ACE

FIG 2

early morning samples, and this they do in the patient group The normals responding to the stress show enhancement of the urinary indices

The target organs responding to adrenal steroids are normally responsive in our patients as has been demonstrated in control and patient groups by the injection of standard doses of Upjohn s lipo adrenal extract (Fig 2) The responses of the adrenal cortex to ACTH is however abnormally sluggish in the patients (Fig 3)

A total response index (abbreviated TRI) has been devised as a measure of adrenal responsivity to our stresses and to hormone injections This consists of a mean of the sum of the per cent changes from prestress or preinjection levels of the two post stress samples of

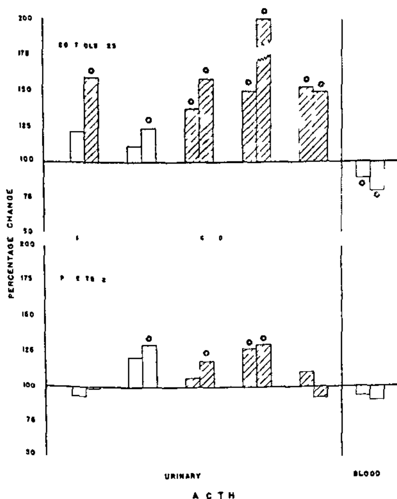


Fig 3

urinary Na, K, uric acid, 17 ketosteroids, and cortins plus twice the two post stress per cent drops in lymphocytes added as positive numbers. For example, all of 25 normal control subjects showed a TRI index of 20 units or greater following 25 mg injections of ACTH, while only 28% of 25 of our schizophrenic patients show a response of 20 units or greater. Table 1 compares TRI values in some of our tests. Approximately this same ratio of normal responders to schizophrenic responders is also found for our various stress tests (last column of table).

Table 1

TOTAL RESPONSE INDEX OF VARIOUS SUBJECTS IN THE STRESS TESTS

Test	*Subjects*	*Mean TRI*	*% of Subjects with Score of 20 or Greater*	*Ratio of Normal Responders to Schizophrenic Responders*
ACTH (Armour)	Normal (25)	46.2	100.0	3.6
ACTH (Armour)	Schizophrenic (25)	12.0	28.0	
Pursuit meter	Normal (46)	22.1	47.8	3.0
Pursuit meter	Schizophrenic (36)	−2.7	15.8	
Targetball	Normal (36)	11.5	32.5	3.3
Targetball	Schizophrenic (20)	−6.7	10.0	
Glucose tolerance	Normal (47)	22.1	48.6	3.2
Glucose tolerance	Schizophrenic (38)	5.7	15.0	

In the schizophrenic group who gave *normal* TRI responses (approximately 1/3 of the total) there is evidence of qualitative abnormalities in comparison to controls in secretion of relative amounts of adrenal steroids concerned with specific metabolic functions. We found no difference in cortin excretion (neutral reducing lipides) in the patient group from the control group and we have compared our other indices of adrenal function which differ in the two groups using cortin excretion as a standard. In Table 2 we express the ratio of mean cortin changes to mean changes in the other variables. The urinary variables in normal men show ratios of 1.30 to 1.38 but the ratios are lower in the patient group. Thus the chronic schizophrenic displays qualitative as well as quantitative abnormalities of adrenal stress responses which appear to lie specifically at the level of the ability of his adrenal cortex to respond to ACTH.

In Table 2 the ratio of mean percentage change in neutral re

ducing lipid output to the mean percentage change in other indices the data are those of the 14 schizophrenic men classified as positive responders (TRI > 20) to the three stress tests and a similar group of normal subjects (see text)

The abnormal responses are not corrected by a vitamin and protein rich diet They are not found in psychoneurotic patients who give normal responses to 25 mg injections of ACTH (Armour) Fig 4 shows data on 12 normal males 11 normal females, 11 psychoneurotic males and 13 psychoneurotic female patients at the Massachusetts General Hospital

The refractoriness of the adrenals to ACTH (Armour) in the patients displaying this phenomenon is not absolute Thus larger quantities of ACTH (75 to 100 mg) produce TRI responses approaching that of the controls given 25 mg doses

Table 2

Response Index	*Ratio*	
	Schizophrenic Men	*Normal Men*
17 Ketosteroid output	1.12	1.35
Uric acid output	0.80	1.38
Potassium output	0.87	1.31
Sodium output	0.94	1.30
Lymphocyte number	0.61	0.82

We have reported that normal persons show an increase of 50 ± 14% in output of 17 ketosteroids in the first 2 hours after rising from a night's sleep This reflects a special form of adrenal stress response associated with waking and starting the day's activities In general schizophrenic patients display as a group a somewhat lower diurnal rhythm of excretion than do normal controls

In 10 female patients suffering from involutional depression we also found evidence of adrenal cortical unresponsivity These patients averaged an insignificant (3%) morning increase in 17 ketosteroid excretion over the night level before they were given a course of electroshock treatments During the treatment course the morning increase in output rose to an average 32% over the night level and it was 25% over the night level a month after the treatments had ended Eight of the 10 women showed good social remission resulting from the treatments Thus we see that adrenal unresponsivity to stress is found in psychotics other than schizophrenics and that the condition improves with therapy

In a recent series of experiments on 9 schizophrenic patients we

have demonstrated that electric shock stimulates adrenal activity to a degree comparable to the injection of approximately 100 mg of ACTH (Armour) Fig 5 compares the response of these patients an hour and a half post injection of 25 mg of ACTH with the response to electric shock across the head sufficient to produce unconsciousness but not strong enough to bring about major convulsion

We have also found that favorable prognosis in electroshock therapy of schizophrenic patients is correlated with the degree of responsivity of the adrenal cortex to pretreatment doses of 25 mg of

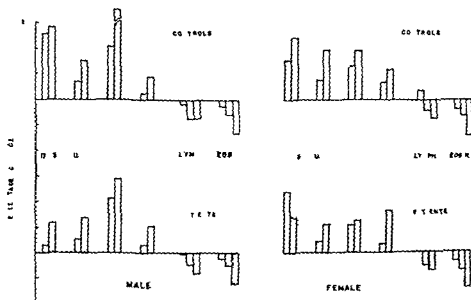


Fig 4

ACTH (r = 0 7 P = 0 02) Fig 6 is a plot of the TRI (horizontally) against the total number of units of improvement on the Malamud rating scale resulting from a course of electroshock therapy Patients indicated by a V were out on visit 2 months post treatment Four out of 5 patients with pretreatment TRI s of greater than 15 were well enough after treatment to leave the hospital on visit The 4 patients with pretreatment TRI values of less than 15 did not improve

We have also found a correlation between adrenal stress response and positive affective components of the patients personality These factors are of prognostic value in insulin treatment i e the patient with the more responsive adrenals is more likely to benefit from insulin treatments

The findings suggest several hypotheses It is possible that all shock therapies (electric, insulin and metrazol) act as repeated vi

olent stresses to discharge excessive amounts of endogenous ACTH which thereby activates the patients sluggish adrenals inducing consequent beneficial metabolic changes To test this hypothesis we have selected 5 schizophrenic patients with relatively responsive adrenals who from our findings would be expected to get well on shock We have given these patients daily injections of ACTH of from 100 to 200 mg Four patient controls receiving placebos were also studied

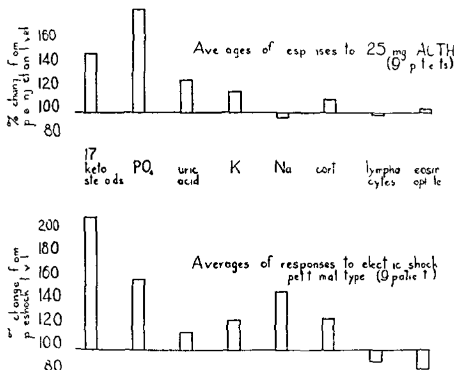


FIG 5

in this series All of the patients were followed by ratings on the Malamud scale

One of the patients had to be dropped from our study after 1 week due to complaint from the family who arrived with a lawyer and a cease and desist order Another of this group was discontinued after a week of injections because of cardiac complications and only 3 of the 4 were carried through 3 full weeks of medication The total psychiatric index registered no significant improvement in 2 of the patients, but 1 showed marked psychiatric improvement in the second and third weeks (100 mg per day) He became less seclusive played games with other patients and engaged in ward work He relapsed the week following treatment

The other two patients treated for 3 weeks showed no net overall improvement though one became euphoric and the other in the second and third week had improvement in insight and his affect went from flat to angry and explosive His mood changed from optimistic to depressed Neither of the patients treated for one week showed changes nor did the ratings of the controls vary significantly

Negative results with so few patients do not disprove our hypothesis that shock therapy may act by releasing large amounts of adrenal hormones via endogenous ACTH discharge since only about

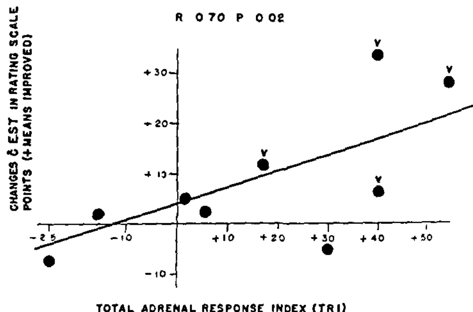


Fig 6

one schizophrenic in three is usually benefited by the shock therapies We wish to test the matter further

We are considering other hypotheses relating the adrenal stress response failure to psychosis We wish to give ACTH (Armour) to schizophrenics whose adrenals are relatively *unresponsive* to stress and to ACTH and our next group of patients just starting on medication has been selected because of their unresponsiveness to ACTH in contrast to our previous group of 5 patients who were selected because of their responsivity

It may be that qualitative abnormalities in adrenal output in schizophrenics in response to ACTH will prevent this substance from being beneficial The repeated use of large doses of specific steroids is also part of our plan of investigation Because of evidence of quali

tative abnormalities of adrenal function in our patient group we think that this approach may prove to be fruitful

DISCUSSION

DR M D ALTSCHULE (McLean Hospital Waverly Mass) Studies on chronically psychotic patients in a mental hospital reveal the following in general irrespective of psychiatric classification

1 Impaired glucose tolerance delayed peak in the curve
2 Insulin resistance
3 Elevated blood lactate level
4 Creatinuria
5 Lowered blood glutathione
6 Decalcification

The above changes resemble the effects of the action of ACTH when the hormone is given to normal subjects this is of interest in view of the fact that ACTH produces mental changes in normal subjects

On the other hand, other changes in adrenal function in psychotic patients in a *mental hospital are not consistent with the action of* ACTH in normal subjects Thus psychotic patients usually have retarded water diuresis and high sweat sodium concentrations indicative of decrease in the amount of electrolyte regulating (DOCA like) steroids The 17 ketosteroid excretion is normal

The initial effect of shock therapy is the release of small amounts of ACTH as shown by changes in leucocytes in uric acid and 17 ketosteroid excretion and in salt and water metabolism but as treatment continues the leucocyte responses wear off and the 17 ketosteroid excretion *falls* below normal Only the changes in salt and water metabolism persist

All of the above *suggests the existence on intimate relation* between chronic psychosis and adrenal cortical function but the nature of this relationship is obscure in general and confusing in detail

The administration of ACTH in psychosis causes normal changes in blood leucocytes in sweat sodium and in 17 ketosteroid secretion Changes in sugar tolerance are often greater than normal Clinical improvement does not occur

DR EDWIN F GILDEA (Washington University School of Medicine St Louis) Metabolic *balance studies have been made on one* schizophrenic young man and one woman who also had hyperostosis frontalis interna in addition to her mental symptoms There was little change in either patient s behavior during the ACTH (Armour) treatment However, the male had an extreme degree of acne vulgaris

prior to treatment which improved markedly during treatment, and the acne practically disappeared by the fifth day With cessation of hormone therapy the acne returned gradually and was about as severe as before 10 days after cessation of treatment Both patients thought they felt better during treatment and there were no disturbing side effects

METHODS

The patients were placed on a well balanced diet of constant composition They were restricted to ward activities and all their urine and feces were collected for 4 days Adrenal reserve glucose tolerance, and insulin tolerance tests were done in the control period Patient E W was given 60 mg of ACTH daily in 4 divided doses for 5 days Patient M S was given 100 mg in 4 divided doses for 5 days They were followed for 7 days during recovery period

Diet

The well balanced diet of these two patients was selected from foods which the patients liked and contained considerable variety from meal to meal but was the same for succeeding days Daily analyses of similar trays prepared at the same time showed remarkable agreement The washings from the dishes showed negligible waste The diets contained the following

	M S	E W
Nitrogen gms	12 5	13 8
NA MEQ	118	108
Cl MEQ	125	115
K MEQ	85	95
Ca gms	85	85
P gms	1 35	1 45
Calories	2200	2400

Water was allowed as desired and there is some uncertainty as to the intake with E W Both patients were up and about They spent some time in Occupational Therapy They were both cooperative and interested in the procedure

RESULTS

The following charts are a summary of the data collected

Metabolic Balance (Fig 7)

The negative calcium + phosphorus balance in the recovery period was mainly due to increased excretion in the feces The negative nitrogen balance during both the experimental and post experi

mental balance periods is noteworthy and was due to urinary excretion

The fluid balance in E W (Fig 8) is only approximate but the decreased fluid excretion during the experimental period is definite in both cases The sustained creatinine excretion in M S during the recovery period might be related to the menstruation which occurred

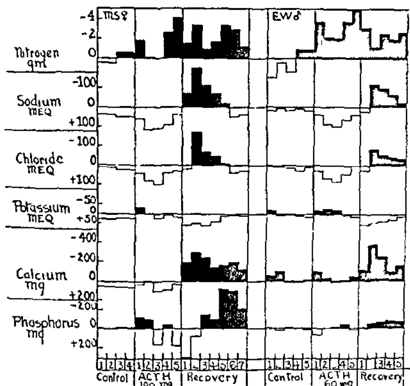


Fig 7 ACTH on metabolic balance

at this time She also excreted small amounts of creatine which increased during the recovery period

E W showed an increase in creatinine during the period of administration of ACTH He showed little creatine at any time

The increase in uric acid excretion was small in patient M S who showed about a 50% drop in blood serum uric acid With subject E W the uric acid excretion during the period of ACTH was doubled and there was a marked drop in serum uric acid 77%

Fig 9 shows changes in hemoconcentration Hb plasma proteins and cell counts W B C = Total — Lymphocytes

The glucose tolerance (Fig 10) was decreased in both patients The capillary-venous difference shows a decreased peripheral utilization on the fourth day of ACTH Insulin resistance was marked in subject M S but not in E W on the fifth day of ACTH

Fifty eight hours after the last hormone injection (Fig 11) the response of the eosinophiles to epinephrine was greatly reduced Even

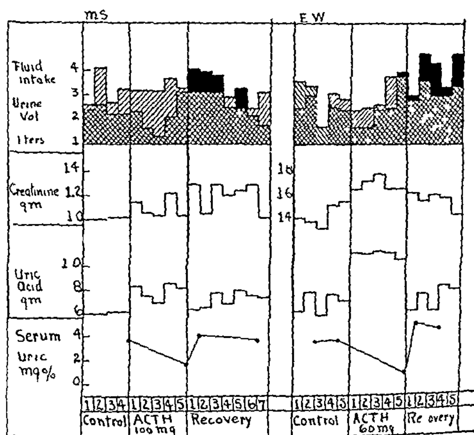


Fig 8 Urine changes ACTH

on the fourth day of recovery in subject M S the response was still less than her control response In E W though his eosinophile count was high there was a normal response on the third recovery day

Both patients showed a typical response to the initial dose of 25 mg of ACTH

Table 3 shows the pertinent data with respect to blood chemistry changes after 5 days of ACTH (Armour) administration and during the post experimental period

Table 3

BLOOD CHANGES

	M S				E W			
	Control	ACTH 5th Day	Recovery		Control	ACTH 5th Day	Recovery	
			2 day	5 day			2 day	5 day
CA mg	11 2	11 2	10 6	11 0	10 7	10 7	10 4	10 1
P mg	3 8	3 3	5 1	3 8	4 1	3 1	3 0	3 9
Na MEQ	130 0	129 0	133 0	127 0	136 0	139 0	—	139 0
K MEQ	3 3	3 1	4 2	3 3	4 5	3 8	—	4 5
Cl MEQ	108 0	113 0	105 0	110 0	106 0	114 0	105 0	109 0
Blood Sugar	70 0	91 0	92 0	72 0	70 0	86 0	70 0	72 0
Cholesterol	265 0	182 0	167 0	260 0	265 0	174 0	156 0	224 0
Uric Acid	3 6	1 6	4 1	3 7	3 7	0 9	4 6	4 4
Plasma Protein	6 7	5 5	6 2	6 8	7 8	6 4	7 0	7 6
Phosphatase Bodansky U	2 9	2 7	2 7	2 7	2 1	[illegible]	2 1	2 1

5th Day % Hormone

Plasma Vol	3040 ml
Blood Vol	4470 ml
Extra Cellular Space	13 4 kg

7th Day After Hormone

Plasma Vol	2400 ml
Blood Vol	4000 ml
Extra Cellular Space	10 0 kg

CASE SUMMARIES—METABOLIC STUDIES LARGELY COMPLETE

E W (Table 3) Male, age 18 Symptoms began 6 months previous to study and consisted of withdrawal from reality hallucinations and paranoid delusions Diagnosis schizophrenia hebephrenic type The patient s symptoms had fluctuated considerably but there was no tendency for consistent remission until after ACTH had been started After cessation of ACTH the patient s condition continued to im prove and later became moderately hypomanic Seven months after treatment he is going to school and relatives consider him better ad justed than previous to onset of his illness

M S (Table 3) This is a 24 year old woman with a long story of chronic physical complaints and anxiety An x ray examination showed hyperostosis frontalis interna Administration of ACTH seemed to increase patient s nervous symptoms rather than diminish them No evidence of feeling of well being or increased activity No indication of increased energy output After cessation of treatment pa tient was a little better and was discharged from hospital but at the present time which is 3 months later, she remains unimproved Di

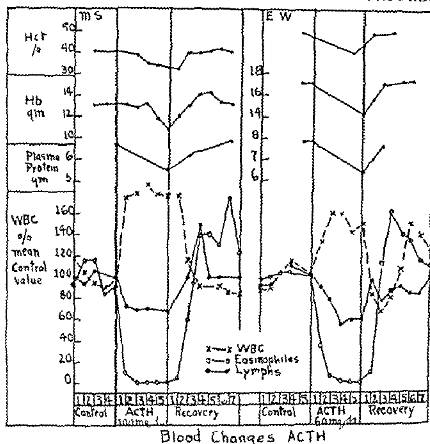


Fig. 9

agnosis: hyperostosis frontalis interna with mixed psychosis including some schizophrenic withdrawal symptoms as well as anxiety and depression.

SUMMARY

Both patients initially showed a normal eosinophile response to epinephrine and had normal glucose and insulin tolerance. The eosinophiles and lymphocytes were reduced markedly by the first 25 mg. injection of ACTH.

Balance studies showed the usual disturbance in electrolyte balance with a retention of Na, Cl and water. The potassium diuresis was slight and was followed by a slight retention which was further increased after the hormone was stopped. Edema was definite in both cases and in M. S. the increase in body weight was accounted for by the increase in extracellular water. The negative Na and Cl balance during the recovery period about balanced the retention during the hormone injection.

In both patients the negative nitrogen balance which started on administration of the hormone continued for several days into the recovery period The total nitrogen loss in M S during the 5 days of ACTH represents the loss of 56 gms of protein with an additional 38 gms lost during the recovery period of 7 days In patient F W the loss of body protein during the ACTH (5 days) administration

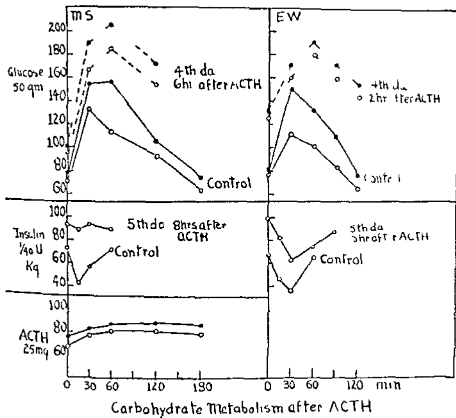


Fig 10

was 106 gms and during the recovery period of 5 days 72 gms were lost

The onset of negative calcium and phosphate balance with ACTH withdrawal was due largely to increase in feces

ACTH caused an increase of about 20 mg % in the fasting blood sugar of both patients The glucose tolerance and peripheral utilization was reduced Some glucose was excreted in the urine in subject M S about 5 gms during the last 3 days of hormone None was excreted by E W Insulin resistance developed in M S but not in E W

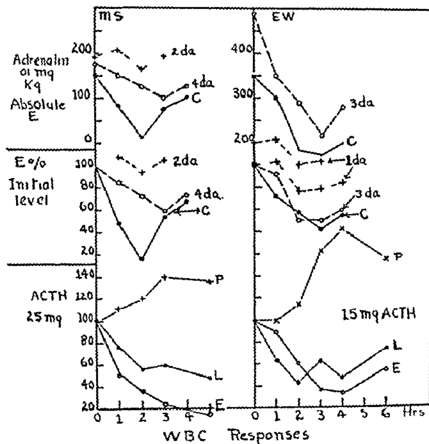


Fig 11

It is of interest that in both cases, eosinophiles increased rapidly on withdrawal of ACTH to values well above the initial control levels At this time 56 hours after the last hormone injection there was a reduced eosinophile response to epinephrine which was still apparent in M S on the fourth day of recovery Since the eosinophiles were ab Bo the last day of ACTH this resistance to epinephrine appears to epitLate a lack of ACTH in the pituitary

It should be noted in Table 3, Blood Changes that there was a marked reduction in serum cholesterol on the fifth day of ACTH There was also a significant fall in uric acid

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Anxiety States Their Response to ACTH and to Isotonic Saline

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As part of the problem of investigating the functioning of the adrenal cortex in psychoneurotic patients we have studied a group of 30 patients hospitalized for an illness in which anxiety was the most prominent feature Each of these patients was given an injection of adrenocorticotrophin (ACTH—Armour) and most of them also were given control injections of isotonic saline The dose of ACTH varied between 2 5 and 25 mgm equivalent of the Armour standard The conclusions that seem indicated by this study are simply that

1) there is a wide individual variation in the response to small doses of ACTH but

2) as the dose increases the degree of response increases and

3) a control injection of saline along with the whole test situation including 4 venipunctures for blood samples also produces a response similar to that given by ACTH in those patients that clinically seem to have the most severe anxiety

As criteria of adrenal cortical activity we have been using changes in a group of indices which at first included

1) an increase in circulating neutrophils
2) a decrease in lymphocytes
3) a decrease in eosinophils, and
4) an increase in the ratio of urinary uric to creatinine

More recently the group of indices of adrenal cortical activity has been extended to include an increase in the excretion of

5) potassium
6) sodium,
7) 17 ketosteroids and
8) neutral reducing lipids

In an attempt to provide a simple yet roughly quantitative

method of describing the amount of activity of the adrenal cortex revealed by any specific index, we have proceeded in the following manner The amount of change in several types of experiments on normals and patients has been plotted, and divided somewhat arbitrarily into 3 categories mild, moderate, and marked These three degrees of change have been given numerical values namely, one half, one and two If this is done for each index in any experiment, and the numerical values for indices are added together we have a more comprehensive measure of adrenal cortical activity This sum of the indices is probably more useful as an indicator of activity than any one index alone because the determination of any of these changes is subject to a variety of possible errors and because we do not understand all the factors involved in a change or lack of change, in any one index

Table 1 lists the range of change in each class, for each of the first 4 indices of adrenal cortical activity mentioned above

Table 1

	0 *Less than*	½ *Between*	1 *Between*	2 *Over*
Neutrophil increase	20%	20–50%	50–150%	150%
Eosinophil decrease	15%	15–20%	20–70%	70%
Lymphocyte decrease	15%	15–20%	20–35%	35%
Uric acid/creatinine increase	45%	45–60%	60–150%	150%

Here the change in each index is expressed as the percentage change from the pretreatment level of that index The possible percentage changes have been grouped into 4 categories zero one half one and two

These categories may be roughly characterized Class zero is that degree of change in the index usually found in normal individuals engaged in ordinary rather sedentary daily work A definite, mild stress or a small dose of ACTH always gives a greater response

Normal individuals at non stressful work rarely react enough to reach class one half and subjects receiving small doses of ACTH almost always react more than this

Class 'one is that range of change in the indices which is never noted in control cases but is common in stress and with ACTH

Class two is a degree of change which is unusual for doses of ACTH not exceeding 25 milligrams

The limits for each of these classes was selected after a study of the reports from Thorn and his associates, and from Elmadjian et al as well as our studies on normals and on cases subjected to mild psychomotor stress

If in any case we add together the number indicating the degree of response of each of the first 4 indices as just outlined we have a sum which could vary from 0 to 8

As more data become available it is highly probable that we shall revise the limits of these classes and increase their number Then perhaps we shall have a sequence of categories enabling us to indicate more closely than at present differences in degree of adrenal cortical activity

Fig 1 shows the scatter of the sum of the first 4 indices plotted

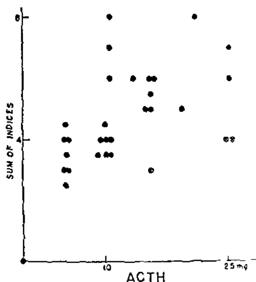


FIG 1

against the dose of ACTH expressed as milligrams equivalent of the Armour standard

The 3 cross marked circles are cases of schizophrenia and are not relevant to this report though their low position is consistent with the findings of other workers (Pincus et al)

What concerns us at the moment is the closed circles which represent the cases of anxiety (Three cases studied after this slide was prepared are not plotted here) It is apparent that the response increases with the dose and that there is wide individual variation

Of these anxiety cases 25 had control injections of saline In almost every case the change in the indices was greater with ACTH than with saline however it is interesting to note that the test situation with the taking of blood and giving of an injection produced in some cases a definite change in the indices All of these patients were hospitalized because of their anxiety state but even so there was some variation in the degree of tenseness anxiety and incapacity as judged

by casual observation and conversation during the conduct of these tests On the basis of this variation in severity of anxiety they were divided into 3 groups

Fig 2 shows the value of the sum of the indices plotted against degree of anxiety Here the least severe anxiety is at the left represented by open circles the moderately severe cases are in the middle, designated by crossed circles the most severe are at the right, indicated by closed circles From this plot one gains the impression that cases which clinically seem to be the most severe anxiety states have the greatest disturbance of these indices of adrenal cortical activity with this test situation

RESPONSE TO SALINE

SUM OF INDICES

DEGREE OF ANXIETY

Fig 2

In the more recent cases tested with both saline and ACTH, we have compared the degree of change in the other indices Our series of cases is small and the evaluation of even statistically significant results must be guarded It is interesting to note, however, that for such doses as we have been using the increase in the rate of excretion of potassium and of neutral reducing lipids (corticoids) after ACTH seems to be significant as noted in Tables 2 and 3

Table 2 deals with the difference in the rate of excretion of potassium during the interval designated We have listed the dose of ACTH the number of cases studied the interval in hours after the injection and the P value (the probability that the difference is due to chance) Table 3 shows the same things for the rate of excretion of neutral reducing lipids (corticoids)

Table 2

POTASSIUM

Dose ACTH	*No of Cases*	*Interval*	*P*
5 2 mg	7	1–3 hr	0
10 4 mg	6	3–5 hr	05
15 6 mg	7	[illegible] hr	02

Table 3

NEUTRAL REDUCING LIPIDS

Dose ACTH	*No of Cases*	*Interval*	*P*
5 2 mg	5	1–3 hr	0
10 4 mg	5	1–5 hr	05
15 6 mg	6	1–5 hr	[illegible]

DISCUSSION

DR J S L BROWNE I would like to comment on two observations in individuals who have been followed with glucocorticoid excretion One woman had had a normal value of about 30 to 40 glycogenic units per 24 hours She had an hysterical attack one afternoon and the next day her corticoids were 200 g u

Another individual was being followed by Dr Venning as a control subject Her glucocorticoids were normal The sister of this woman became very ill and the woman naturally became upset The corticoids promptly rose to nearly 300 g u

Thus ordinary life situations producing psychological stresses can fire the adrenal as effectively as can burns or fractures Once the adrenal has been fired presumably the consequences are the same and thus psychological situations may influence such diseases as rheumatoid arthritis etc

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RESPONSE TO SALINE

SUM OF INDICES

0

2

4

DEGREE OF ANXIETY

Fig 2

In the more recent cases tested with both saline and ACTH, we have compared the degree of change in the other indices Our series of cases is small and the evaluation of even statistically significant results must be guarded It is interesting to note however, that for such doses as we have been using the increase in the rate of excretion of potassium and of neutral reducing lipids (corticoids) after ACTH seems to be significant as noted in Tables 2 and 3

Table 2 deals with the difference in the rate of excretion of potassium during the interval designated We have listed the dose of ACTH the number of cases studied the interval in hours after the injection and the P value (the probability that the difference is due to chance) Table 3 shows the same things for the rate of excretion of neutral reducing lipids (corticoids)

Table 2

POTASSIUM

Dose ACTH	*No of Cases*	*Interval*	*P*
5 2 mg	7	1–3 hr	0[illegible]
10 4 mg	6	5–5 hr	0[illegible]
15 6 mg	[illegible]	3–5 hr	0?

Table 3

NEUTRAL REDUCING LIPIDS

Dose ACTH	*No of Cases*	*Interval*	*P*
5 2 mg	5	1–5 hr	0
10 4 mg	5	1–5 hr	0
15 6 mg	6	1–5 hr	[illegible]

DISCUSSION

DR J S L BROWNE I would like to comment on two observations in individuals who have been followed with glucocorticoid excretion One woman had had a normal value of about 30 to 40 glycogenic units per 24 hours She had an hysterical attack one afternoon and the next day her corticoids were 200 g u

Another individual was being followed by Dr Venning as a control subject Her glucocorticoids were normal The sister of this woman became very ill and the woman naturally became upset The corticoids promptly rose to nearly 300 g u

Thus ordinary life situations producing psychological stresses can fire the adrenal as effectively as can burns or fractures Once the adrenal has been fired presumably the consequences are the same and thus psychological situations may influence such diseases as rheumatoid arthritis etc

by casual observation and conversation during the conduct of these tests On the basis of this variation in severity of anxiety they were divided into 3 groups

Fig 2 shows the value of the sum of the indices plotted against degree of anxiety Here the least severe anxiety is at the left, represented by open circles the moderately severe cases are in the middle, designated by crossed circles the most severe are at the right, indicated by closed circles From this plot one gains the impression that cases which clinically seem to be the most severe anxiety states have the greatest disturbance of these indices of adrenal cortical activity with this test situation

RESPONSE TO SALINE

SUM OF INDICES

DEGREE OF ANXIETY

Fig 2

In the more recent cases tested with both saline and ACTH, we have compared the degree of change in the other indices Our series of cases is small and the evaluation of even statistically significant results must be guarded It is interesting to note however, that for such doses as we have been using the increase in the rate of excretion of potassium and of neutral reducing lipids (corticoids) after ACTH seems to be significant as noted in Tables 2 and 3

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15 6 mg	7	5–5 hr	0 2

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NEUTRAL REDUCING LIPIDS

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DISCUSSION

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Thus ordinary life situations producing psychological stresses can fire the adrenal as effectively as can burns or fractures Once the adrenal has been fired presumably the consequences are the same and thus psychological situations may influence such diseases as rheumatoid arthritis etc

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The Role of the Adrenal Gland in Alcoholism

James J Smith

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From our laboratory and clinical studies of alcoholics during the past several years we have been forced to conclude that alcoholism is a metabolic disease Although alcoholism manifests itself in society primarily as a behavior problem it occurred to us that perhaps the behavior disturbance was not the disease itself but merely a symptom of the underlying metabolic processes Thus it is our conception that contrary to popular and psychiatric opinion, the behavior disturbance of the alcoholic is not a response to difficulties in the external environment but to metabolic difficulties in the internal environment

It has been apparent to us for some time that acute alcohol poisoning and the repeated alarm stimuli associated with alcoholism lead to various stages of adrenal cortex insufficiency In fact delirium tremens one of the possible end stages of alcoholism and Addisonian crisis the end stage of adrenal cortex hypofunction are biochemically and clinically quite similar The treatment for both delirium tremens and Addison s disease has been shown to be fundamentally that of supplying sodium chloride and glucose These observations in delirium tremens which occurs only in chronic alcoholics are readily explicable in terms of the adaptation syndrome That alcohol does cause adrenal stimulation we have shown by the fall in adrenal ascorbic acid elicited by giving alcohol to rats

On the basis of this reasoning we have treated patients in acute alcoholism patients in delirium tremens and chronic alcoholics with aqueous adrenal extract lipoadrenal extract desoxycorticosterone testosterone and recently ACTH with results which I will now describe In my discussion I will confine myself to the description of the results we have obtained both biochemical and clinical in the treatment of 3 states of acute alcoholism Korsakoff psychosis acute alcohol intoxication and delirium tremens All these patients received 25 mg ACTH intramuscularly every 6 hours around the clock for the treatment period indicated in the illustrations These patients re

ceived no other supportive measures or medication before or during the ACTH treatment period and sedation was withheld

Two patients with Korsakoff psychosis were treated with ACTH without clinical improvement Following treatment with 175 mg ACTH without beneficial effect one of these patients was given adrenocortical extract in doses of 10 cc intravenously every 6 hours around the clock, for 36 hours This patient improved markedly on treatment with adrenocortical extract within 24 hours Our criteria for evaluating improvement are given in Fig 1

As will be seen the criteria are quite objective and significant

CLINICAL CRITERIA	NO. PTS.	CONVENTIONAL HRS TREATED 12	18	24	36	ACE HRS TREATED 12	18	24	36	ACTH HRS TREATED 12	18	24	36
MEMORY DEFECT	+++	++++	++++	++++	++++	++++	++++	++	++	++++	++++	++++	++++
CONFABULATION	++++	++++	++++	++++	++++	++++	++	0	0	++++	++++	++++	++++
AUDITORY VISUAL HALLUCINATIONS	++++	++++	++++	++++	++++	++++	++	0	0	++++	++++	++++	++++
DISORIENTATION TIME	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++
DISORIENTATION PLACE	++++	++++	++++	++++	++++	++++	++++	0	0	++++	++++	++++	++++
DISORIENTATION PERSON	++++	++++	++++	++++	++++	++++	0	0	0	++++	++++	++++	++++
RESTLESS EXCITEMENT	++++	++++	++++	++++	++++	+++	+	0	0	++++	++	++	+

0 ABSENT + SLIGHT ++ MODERATE +++ SEVERE ++++ EXTREME

Fig 1 Effect of treatment on Korsakoff psychosis

It is not surprising that the conventional treatment of Korsakoff psychosis results in no improvement inasmuch as it consists at most in sporadic doses of vitamins and sedation if the patient becomes too boisterous It will be seen that the only thing that improved in the patients given ACTH was some diminution in restless excitement On the other hand it will be seen that improvement in the Korsakoff psychosis is apparent within 18 hours and well established at the end of 24 hours in the patient given ACE

While ACE and ACTH are both effective in the treatment of acute alcoholism there are differences of efficacy according to age and sex Furthermore ACE in our experience has a much more prompt sedative effect than ACTH and it seems to abolish anorexia somewhat more quickly ACTH abolishes sweating and visual hallucinations somewhat more promptly than ACE Otherwise as indicated in

great rise I can say this on the basis of 17 ketosteroid determinations done on 70 male alcoholics and 35 female alcoholics In both of these series the 17 ketosteroid values as an average, were only slightly below normal

I would like to point out here that there are gaps in our tables, chiefly in urinary constituents, because of the peculiar circumstances under which we work The patients described throughout are all on the psychiatric service some of them are on the "violent wards and the collection of specimens particularly in the earlier stages of their alcoholism is at times impossible It is testimony to the efficacy of the treatment used that the patients are sufficiently composed to collect good 24 hour urines for ketosteroid determinations following treatment

The clinical and biochemical effects of ACTH in delirium tremens are set forth in Figs 4 and 5 In this syndrome ACTH is strikingly beneficial, and superior to ACE or ACE and desoxycorticosterone, or conventional treatment This is quite interesting, because clinically and biochemically delirium tremens is quite similar to Addisonian crisis or adrenal exhaustion We had thought that delirium tremens which occurs only in chronic alcoholics, was an expression of the adaptation syndrome Theoretically and on the basis of our finding that alcohol given to rats causes a marked depression of the adrenal ascorbic acid we had postulated that the repeated stimuli of drinking probably led to adrenal exhaustion It is well known that delirium tremens is precipitated in chronic alcoholics even when they are *not* drinking by such stresses as trauma, surgical operations and acute infections Despite these cogent indications of an exhausted adrenal gland in delirium tremens, we have the clinical fact that alcohol *will* improve these patients for a brief period I should like to state emphatically that we never give alcohol to patients in either acute alcoholism or delirium tremens In Europe, and particularly in France and Switzerland intravenous alcohol is given in delirium tremens with reputed good results

It was on the basis of this clinical experience that we gave ACTH to patients with delirium tremens Although the effect of ACTH in delirium tremens is quite striking, as shown in Fig 4, the patients themselves showed marked improvement which does not appear on the chart One of the patients (J) had pneumonic consolidation of three quarters of his right lung concomitant with his delirium tremens He was on the "violent" ward Within 2 to 3 hours of his having been given 25 mg of ACTH he was sufficiently composed to be transferred to the medical ward He continued to improve rapidly and he is the patient whom I described in commenting on Dr Finland's paper Despite his persistent pneumonic consolidation and

despite our concern with it he was up and about the ward as if he had just gotten over a cold, within 36 hours

Another of our patients (M) showed the hyperpyrexia which we frequently see in delirium tremens Although his temperature was 109 6°, he had begun to make definite improvement within 10 to 12 hours and he progressed rapidly to recovery There is a much higher mortality among patients with hyperpyrexia in delirium tremens than in patients with delirium tremens who have little or no fever

In evaluating the efficacy of treatment in delirium tremens it is

CLINICAL CRITERIA	NO PT	CONVENTIONAL				ACE				ACTH			
		HRS TREATED				HRS TREATED				HRS TREATED			
		6	12	18	24	6	12	8		6	12	18	4
AUDITORY VISUAL HALLUCINATIONS	+++	++++	+++	+++	++++	+++	++	+	0	+	+	0	0
OCCUPATIONAL HALLUCINOSIS	+++	++	+++	+++	+++	++	+	0	0	+	0	0	0
DISORIENTATION TIME	++++	++++	++++	+++	++++	+++	++	++	+ 0	+	+	+	0
DISORIENTATION PLACE	++++	++++	++++	++++	++++	++++	++	++		+++	++	0	0
DISORIENTATION PERSON	++++	++++	++++	++++	+++	+++	++	++	+	+	+	0	0
SHOUTING + HYPERKINESIS	++++	++++	++++	++++	++++	++	+	0	0	+	0	0	0
TREMULOUSNESS	++++	++++	++++	++++	++++	++	+	0	0	+	0	0	0
SWEATING	++++	++++	++++	++++	++++	++	+	0	0	++	0	0	0
FEAR	++++	++++	++++	++++	++++	++	0	0	0	++	0	0	0

0 ABSENT + SLIGHT ++ MODERATE +++ SEVERE ++++ EXTREME

Fig 4 Effect of treatment on delirium tremens

important to keep in mind that the period of time over which recovery takes place is the cardinal consideration After all the patient with delirium tremens who is not suffering an overwhelming infection and who is treated properly should get well within 48 to 72 hours By the conventional treatment I refer to the use of generous dextrose and saline infusions combined with ascorbic acid nicotinic acid and sedation On ACTH however, we begin to notice improvement within 3 to 10 hours and the improvement is clinically more striking It is important to remember that no other supportive measures or medications were used and that sedation was not given

In Fig 5 it will be noted that there was a trend to low serum potassium Patient M was remarkable for his high serum uric acid I have

great rise I can say this on the basis of 17 ketosteroid determinations done on 70 male alcoholics and 35 female alcoholics In both of these series the 17 ketosteroid values, as an average, were only slightly below normal

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		6	12	18	24	6	12	8	4	[illegible]	12	18	[illegible]
AUDITORY VISUAL HALLUCINATIONS	++++	++++	++++	++++	++++	++	++	+	0	+	+	0	0
OCCUPATIONAL HALLUCINATIONS	++++	++++	++++	++++	++++	++	+	0	0	+	0	0	0
DISORIENTATION TIME	++++	++++	++++	++++	++++	+++	++	++	+ 0	+	++	+	0
DISORIENTATION PLACE	++++	++++	++++	++++	++++	++++	+++	++	+	+++	++	0	0
DISORIENTATION PERSON	++++	++++	++++	++++	++++	++++	+++	++	+	++	+	0	0
HALTING + HYPERKINESIS	++++	++++	++++	++++	++++	++	+	0	0	+	0	0	0
TREMULOUSNESS	++++	++++	++++	++++	++++	++	+	0	0	+	0	0	0
SWEATING	++++	++++	++++	++++	++++	++	+	0	0	++	0	0	0
FEAR	++++	++++	++++	++++	++++	++	0	0	0	++	0	0	0

0 ABSENT + SLIGHT ++ MODERATE +++ SEVERE ++++ EXTREME

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PATIENT	HRS TREATED	SERUM NA mEq/L	SERUM K mEq/L	SERUM URIC ACID mg%	SERUM CA mg%	γ GLOBULIN mg%	TOTAL LIPIDS mg%	WBC per cu mm	LYMPHOCYTES per c mm	URINARY NA mEq/L	URINARY K mEq/L	URINARY CA mg%	u/c	URINARY 17 KETO STEROIDS mg/24 hrs
B	0	136	462	69	1038	167	725	6800	2142	100	196	317	032	
♂ 36	6	134	478	65	1174	188	755	5500	1760	79	100	096	028	
	12	132	494	·5	1183	170	725	6050	1421	8	92	—	032	
RECOVERY	18	—	—	59	1048	167	685	6850	890	—	90	—	024	FOR 24 HRS ō ACTH
	24	139	477	48	970	170	675	5750	862	—	—	—	—	96
J	0	—	—	—	—	—	—	7600	684	-	-	-	046	
♂ 43	6	130	368	463	938	068	530	4500	450	-		-	086	
	12	-	384	363	1021	068	470	5150	669	-	-	025	081	
RECOVERY	18	-	418	376	1030	068	470	5200	260	-	-	025	064	FOR 24 HRS ō ACTH
	24	-	418	410	948	063	565	5800	319	-	-	025	038	71
L	0	130	305	30	988	11	630	3500	1225	-	-	—	-	
♂ 43	6	124	297	24	969	10	625	3050	640		-	93	080	FOR 24 HRS ō ACTH
	12	127	360	22	806	11	675	2650	556	100	45	14	131	69
RECOVERY	18	130	349	21	884	10	650	3150	-	117	29	097	-	
	24	141	525	21	922	11 10	670 DAYS	5200 AFTER	1144 ACTH		4	040	055	118
M	0		360	145	949	095	530	4200	756	-			-	
♂ 39	6	160	353	141	939	11	615	4500	877					
	12		341	148	930			3400	629	-			-	
RECOVERY	18				-			3500	420	-	-	025	-	FOR 24 HRS ō ACTH
	24	-	328	136	763			6200	465		-	030		24

Fig 5 Effects of ACTH in delirium tremens

noted a similarly high serum uric acid in another patient with hyperpyrexia (temperature 110°) and I do not know whether this is a function of patient M s delirium tremens or hyperpyrexia The 17 ketosteroid excretion in the 24 hour period following treatment with ACTH is seen to be definitely low in all patients and particularly in patient M (2 4 mg)

We have several chronic alcoholics under treatment with ACTH but it is too early to draw conclusions in this group of patients

I should like to include as controls a miscellaneous group of patients who received doses of ACTH comparable to those given above None of these control patients showed clinical improvement on ACTH These were one patient with agitated depression one patient with intractable insomnia three patients with post partum psychosis (these patients did not respond to ACE either but the psychosis of one cleared quickly on progesterone and the psychosis of another responded slowly to progesterone) one patient with generalized dermatitis from either penicillin or sulfonamides who developed concomitantly with his skin rash a manic psychosis This was considered to be a toxic psychosis and although his skin rash subsided his mania persisted unabated on treatment with ACTH

In summary then it appears from our limited series that whereas ACE is effective in Korsakoff psychosis ACTH is not that both ACE and ACTH are effective in the treatment of acute alcohol intoxication In this condition ACE is probably preferable because of its greater sedative action In delirium tremens ACTH is easily the most effective treatment we have used and is superior to conventional treatment and the use of ACE

DISCUSSION

DR JAMES J SMITH One thing I had on the charts and hoped to be able to show I would like to tell you verbally and that is about the ketosteroid excretion in the acute alcoholics with delirium tremens The ketosteroids in general in patients with delirium tremens certainly didn t rise after ACTH The patient who had the temperature of 109 6° had 2 4 mgs ketosteroids in the succeeding 24 hours and in general his ketosteroid value as with the other patients was much lower than we get for our average alcoholics In 70 male alcoholics we have gotten in general 17 ketosteroid values slightly below normal

DR GEORGE W THORN One can employ the nonspecific euphoric response to ACTH that is the improved general sense of well being improved appetite very effectively in patients with anorexia nervosa

PATIENT	HRS TREATED	SERUM NA mEq/L	SERUM K mEq/L	SERUM URIC ACID mg %	SERUM CA mg %	γ GLOBULIN mg %	TOTAL LIPIDS mg %	W B C per cu mm	LYMPHOCYTES per mm	URINARY NA mEq/L	URINARY K mEq/L	URINARY CA mg %	u/c	URINARY 17 KETO STEROIDS mg/24 hrs
B	0	136	4 62	69	1038	1 67	725	6800	2,142	100	196	317	0 32	
♂ 36	6	134	4 78	6 5	11 74	1 88	755	5500	1760	79	100	0 96	0 28	
	12	132	4 94	6 5	11 83	1 70	725*	6050	1421	8	32	—	0 32	
RECOVERY	18	—	—	59	10 48	1 67	685	6850	890	—	90	—	0 24	FOR 24 HRS p ACTH
	24	139	4 77	48	9 70	1 70	675	5750	862	—	—	—	—	9 6
J	0	—	–	–	–	–	–	7600	654	–	–	–	0 46	
♂ 43	6	130	3 68	463	938	0 68	530	4500	450				0 86	
	12	–	3 84	363	1021	0 68	470	5150	669	–	–	025	0 81	
RECOVERY	18	–	4 18	376	1030	0 68	470	5200	260	–	–	025	0 64	FOR 24HRS p ACTH
	24	–	4 18	410	948	0 63	565	5800	319	–	–	025	0 88	7 1
L	0	130	3 05	30	988	1 1	630	3500	1225	–	–	–	–	
♂ 43	6	129	2 97	24	969	1 0	625	3050	640		–	93	0 80	FOR 24HRS. p ACTH
	12	127	3 60	22	806	1 1	675	2650	556	100	45	1 4	1 31	6.9
RECOVERY	18	130	3 49	21	884	1 0	650	3150	–	117	29	097	–	
	24	–		21	922	1 1	670	5200	1,144		4	040	0 55	
		41	5 25			10	DAYS	AFTER	ACTH					11 5
M	0		3 60	145	949	0 95	530	4200	756	–			–	
♂ 39	6	160	3 53	141	939	1 1	615	4500	877		–			
	12		3 41	148	930			3400	629	–		–	–	
RECOVERY	18							3500	420	–	–	025	–	FOR 24HRS. p ACTH
	24	–	3 28	136	763			6200	465	–	–	030	–	24

Fig 5 Effects of ACTH in delirium tremens

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Effects of Adrenocorticotrophic Hormone of the Pituitary Gland on Neuro-muscular Function in Patients with Myasthenia Gravis*

Clara Torda and Harold G Wolff

THE NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL SCHOOL
NEW YORK CITY

Administration of the adrenocorticotrophic hormone of the pituitary gland (ACTH) to patients with myasthenia gravis was first started by Torda and Wolff in 1944 (*Proc Soc Exper Biol and Med* 1944, **57** 137) on the basis of the following observations and inferences (1) The immediate cause of the symptoms of myasthenia gravis is a decrease of acetylcholine synthesis (2) administration of ACTH (Armour) increases acetylcholine synthesis *in vivo* (3) increase of the lymphatic tissue (round cell infiltration of various organs mainly striated muscle) and hyper function thymus have been found in patients with myasthenia gravis Tissue fractionation studies have shown that one of the sources of the substances that inhibit acetylcholine synthesis is the thymus Administration of ACTH induces a reduction in the mass of the thymus and the lymphatic tissue (4) removal of the pituitary gland in rats induces changes in the electromyogram that closely resemble abnormalities noted in patients with myasthenia gravis (5) the pituitary gland of several patients who died of myasthenia gravis showed accumulation of eosinophilic colloid material suggesting altered function of the gland

In 1948 Soffer and collaborators reported without objective testing remission of the symptoms in a patient moderately ill with myasthenia gravis when ACTH (Armour) was administered In 1949 Hellman reported impairment of patients with myasthenia gravis during the period of ACTH (Armour) injections Since 1948 ACTH has

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These patients with extreme weight loss can often be stimulated over the first few days of ACTH treatment to eat more vigorously and their general health may be improved sufficiently for them to be capable of benefiting from psychiatric aid

DR JAMES J SMITH I think the point about water metabolism is quite appropriate We find that particularly after delirium tremens the patients may not excrete any more than 300 or 400 cc in the succeeding 24 hours and we don t know whether we get a specific ACTH effect or whether we may get the same effect by retaining fluid that we would have gotten had we given them an infusion However, it is important to keep in mind that we get much more prompt clinical improvement in patients in delirium tremens given ACTH than we get no matter how generously we infuse them without ACTH

I might say that we did not infuse any of these patients We didn t give them Vitamin C pantothenic acid or any of the other vitamins that might work in conjunction with ACTH or cortical extract

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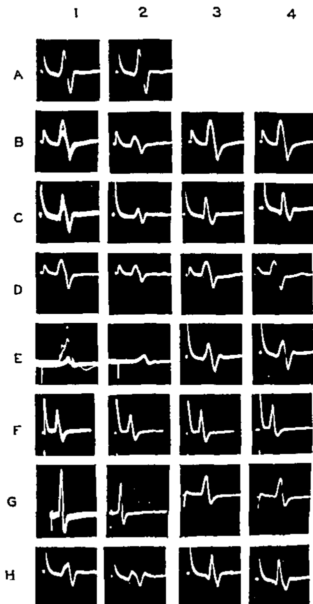


Fig 1 Column 1 represents action potential records taken at the beginnings of the 30 second stimulation period with a stimulus of a frequency of 10 per second Column 2 represents records taken at the end of the 30 second stimulation period without moving the electrodes

First row of slide 1 represents records taken from a control subject The amplitude of the muscle action potential was maintained unaltered during the stimulation period

Rows B to H represent records taken from the various patients The action potential decreased significantly within the first few pulses of stimulation and was maintained at this low level thereafter Row F represents records of the patient least sick with myasthenia gravis

been administered to patients with myasthenia gravis in several hospitals and to date 8 patients received ACTH (Armour) at the New York Hospital

The patients were men and women from 24 to 55 years of age and had had myasthenia gravis from 2 to 17 years They received a total of from 300 to 45 mg of neostigmine bromide per day The most severely ill patient was unable to walk without attendance All patients had had in different degree of severity a generalized weakness ptosis of the eye lid weakness and easy fatigability of the muscles of the palate, tongue face deglutition arms and legs During the 2 years before this special study the patients had experienced minor transient fluctuations but no significant changes in their clinical state

The following tests were performed before administration of ACTH

1 Electromyography

Muscle action potential records were taken during indirect percutaneous stimulation of the ulnar nerve These records were taken once a day the same time of the day and 3 hours after the last medication was taken One recording electrode was placed on the hypothenar eminence and the other on the ventral surface of the first phalanx of the fifth finger The ulnar nerve was stimulated over the elbow with 10 and 30 pulses per second for at least 30 seconds The stimulus had a duration of one millisecond and was of supramaximal intensity The patients except for one showed the abnormalities noted in patients severely or moderately ill with myasthenia gravis namely the muscle action potential decreased on repetitive indirect stimulation This decrease occurred within a few pulses of stimulation and was more marked on stimulation with 30 pulses per second than with 10 pulses per second at the end of a 30 second stimulation period Although daily variations in the amount of decrease of the muscle action potential occurred the decrease was always over 35% One patient had almost normal action potential as is commonly observed in patients mildly sick with myasthenia gravis (Fig 1)

Records in columns 3 and 4 were taken the third day after administration of the hormone By that time the intake of neostigmine was reduced and not 3 but from 6 to 15 hours elapsed between the last intake of neostigmine bromide and the recording of the action potential

Column 3 represents records taken at the beginnings of the 30 second stimulation period with 10 pulses per second and column 4 records taken at the end of the 30 second stimulation period without moving the electrodes The amplitude of the action potential was maintained unaltered similarly to healthy persons

Records of columns 1 and 3 cannot be compared since the position of the recording electrodes could not be duplicated exactly on following days

2 Ergography

For this test a spring ergograph was used The spring was stretched 2 5 cm once a second by the index and middle finger of the right hand exerting a tension of 15 kg The patients were asked to move the spring until occurrence of severe fatigue The work performance of the pa

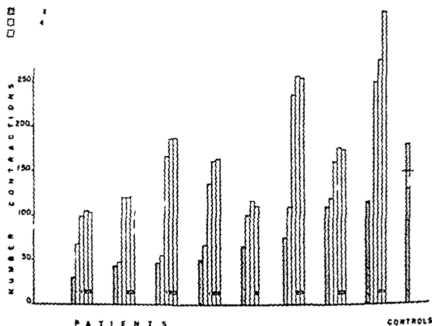


FIG 2 The shaded columns represent observations before administration of ACTH These columns are much shorter than the column representing the work performances of female controls The work performance of male controls is approximately 3 times that of females The empty columns represent the average work performance during administration of ACTH A slight increase in performance was noted Columns 1 2 and 3 represent average performances during the first 4 days, the fourteenth day and the forty fifth day after completion of administration of ACTH respectively The performance increases for about 5 to 7 days after the last injection of ACTH and is maintained, with great variations thereafter

tients, with the exception of the one mentioned before remained below 30% of the work performance of control subjects of the same sex and age group (Fig 2)

3 Acetylcholine Synthesis

In the presence of serum from patients with myasthenia gravis the synthesis of acetylcholine is decreased This decrease seems to be specific for myasthenia gravis and the more severe the myasthenia gravis the less acetylcholine is synthesized The test consists of incuba

tion of the serum of a patient with a tissue containing cholineacetylase and testing the resulting mixture for the amount of acetylcholine synthesized The synthesis of acetylcholine in the patients was decreased from 25 to 55% over normal controls (Fig 3)

After a one week observation period the patients received ACTH given in amounts of from 20 to 25 mg every 6 hours for 5 days The patients experienced some malaise headache occasional abdominal cramps rounding of the face some respiratory difficulties and some changes of the electrocardiogram

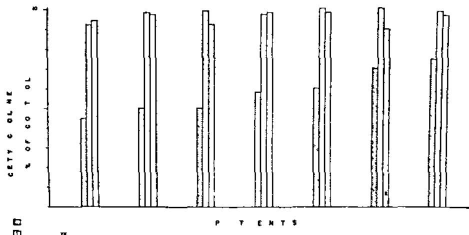


FIG 3 The shaded columns represent the amount of acetylcholine synthesized in percentage of control in the presence of serum from the patients taken before injection with ACTH Columns 1 represent the amount of acetylcholine synthesized 3 days after the last injection of ACTH Columns 2 represent the amounts of acetylcholine synthesized 2 months after the last injection of ACTH

These disturbances became more evidenced toward the end of the administration of ACTH and for one or two days after the last injection of ACTH Thereafter these symptoms disappeared and remission of the symptoms of myasthenia gravis occurred

The improvement of the patients consisted in decrease of the weakness and the easy fatigability of the muscles and an increase of the appetite and a reduced requirement of neostigmine bromide This improvement has been maintained for many months

The measurable components of the improvement were as follows

1 Electromyograph

The ability to maintain the amplitude of muscle action potential during repetitive indirect stimulation returned during the period of

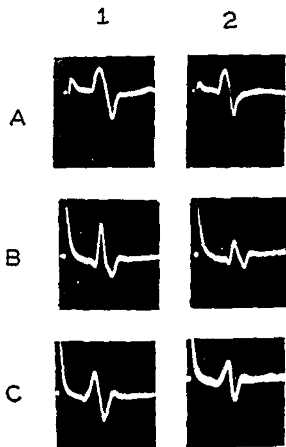


Fig 4 Column 1 represents records taken from rate at the beginning of a 30 sec stimulation period with 30 pulses per second Column 2 represents records taken at the end of a 30 second stimulation period Row A represents records taken from a control rat The amplitude of the action potential decreased 10% Row B represents records taken from a hypophysectomized rat The amplitude of the action potential decreased during the first pulses of stimulation by 60% and was maintained at the lower level for the rest of stimulation Row C represents records taken from an ACTH injected hypophysectomized rat The amplitude of the action potential decreased 20% during the 30 second stimulation period

administration of ACTH to normal and was so maintained during the time elapsed between administration of ACTH and the present report (from 4 to 10 mo) (Fig 1)

2 Myography

The performance on the spring ergograph increased significantly during and after administration of ACTH Improvement of performance was maintained with great fluctuations, during the time

elapsed between administration of ACTH and the present report (Fig 2)

3 Acetylcholine Synthesis

The ability of serum of patients to support acetylcholine synthesis increased during administration of ACTH and approximated normal values from the fourth day of administration of ACTH up to date (Fig 3)

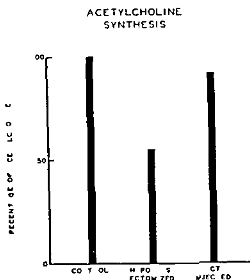


Fig 5 Column 1 represents the amount of acetylcholine synthesized by control brains expressed as 100% Column 2 represents the amount of acetylcholine synthesized by brains of hypophysectomized rats (averaging 56% of the control) Column 3 represents the amount of acetylcholine synthesized by ACTH injected hypophysectomized rats (averaging 91% of the control)

The mechanism of action of ACTH in patients with myasthenia gravis is not yet known It is known that the action potential of hypophysectomized rats is similar to the action potential of patients severely ill with myasthenia gravis After administration of ACTH to hypophysectomized rats the action potential returns to normal (Fig 4)

The amount of acetylcholine synthesized by brains of hypophysectomized rats is significantly less than the amount synthesized by control brains After administration of ACTH the ability of brains of hypophysectomized rats to synthesize acetylcholine approximated normal values (Fig 5) Administration of ACTH to healthy rats in

creased the ability of brain to synthesize acetylcholine far above normal values

Conclusion

An improvement of the clinical state and of the performance with objective tests were observed in 8 patients with myasthenia gravis after administration of ACTH This remission has been variable and incomplete and is of uncertain but considerable duration

DISCUSSION

DR WILLIAM Q WOLFSON A patient with myasthenia gravis whom we studied may be of interest because he received both ACTH and pregnentriolone* and also because he showed certain peculiarities in his hematological responses to ACTH Fig 6 summarizes the clinical observations In August 1949 he required 435 mg of prostigmine daily for maintenance During a four day period he received 450 mg of pregnentriolone The initial response seemed encouraging with a drop in prostigmine requirement to 130 mg /day This, however, was not sustained nor was it accompanied by the improvement in head lifting later seen following ACTH After pregnentriolone was discontinued the daily prostigmine requirement continued to rise and eventually reached 345 mg day Because of Ungar s report that, in the guinea pig pregnentriolone released splenin A from the spleen which in turn decreased bleeding time an attempt was made to see if this steroid had similar effects in man Neither in this patient, nor in a second patient did pregnentriolone produce significant changes in bleeding time or platelet count

In early October the patient was readmitted for study with ACTH Potassium chloride (9 0 gm day) was begun shortly before ACTH and appeared to cause some clinical improvement with a decrease in daily prostigmine requirement from 345 mg /day to 255 mg day On each of 8 successive days the patient received 25 mg of ADACTAR a long acting ACTH preparation During its administration his clinical condition did not change

On the second day after ACTH was withdrawn there was definite improvement in head lifting and the prostigmine requirement decreased to 120 mg day Thereafter as in the patients studied by Dr Torda and Dr Wolff the prostigmine requirement continued to decrease for a time and head lifting continued to improve Over one month has now elapsed since ACTH was discontinued His muscular

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*The pregnentriolone (4 pregnene 17B 20a 21 triol 3 one) used in these studies was furnished through the cooperation of Dr Ernst Oppenheimer and Dr Fred E Houghton of the Research Division Ciba Pharmaceutical Products Summit N J

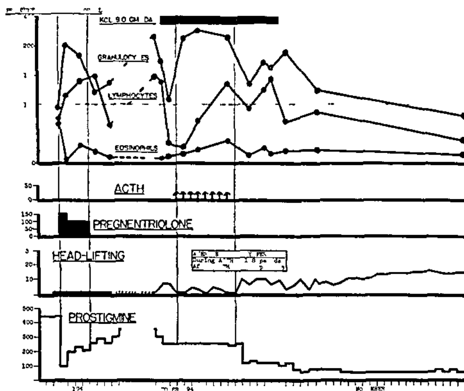


FIG 6 Typical clinical response and atypical hematological response to ACTH in a patient with myasthenia gravis

strength as indicated by head lifting continues to be much superior to that before ACTH administration and his prostigmine requirement has become stabilized at between 60 and 90 mg /day At least for the moment this state appears relatively stable It is interesting that the improvement in head lifting was considerably more gradual than the decrease in prostigmine requirement and to some degree there was an impression that these were partially independent variables

Despite this clinical course which closely conforms to that of patients studied by Drs Torda and Wolff his hematological responses to treatment were most unusual When first seen in August his eosinophil count was low normal 103 per cu mm Six hours after the first dose of pregnentriolone the value had fallen to 3 per cu mm Thereafter during pregnentriolone administration the eosinophil count rose to a maximum of 44 per cu mm and when pregnentriolone was withdrawn the count fell to 15 per cu mm The lymphocytes also were increased during pregnentriolone administration and fell when it was withdrawn

Since the first dose of pregnentriolone was given the eosinophil count has never exceeded 56 per cu mm On the days immediately before he was given ACTH, the eosinophil counts averaged 12 per cu mm During ACTH administration the count rose to 56 per cu mm and promptly again dropped to 19 per cu mm when ACTH was withdrawn During the second week after ACTH withdrawal the count became stable at about 28 per cu mm Somewhat similar changes occurred in lymphocyte counts

In only two conditions so far described does eosinophilia appear to be compatible with a satisfactory clinical response to ACTH In skin sensitization, ACTH administration may increase the eosinophil count, but the counts found in such patients are high, rather than low, and lymphopenia occurs in response to ACTH In disseminated lupus erythematosus, extremely low initial eosinophil counts have been reported, and, in the one patient we studied the basal count was 0 to 3 per cu mm This appears to represent involvement of the eosinophils in the pancytopenia frequently present in lupus As the patient shows improvement, the eosinophil count may rise because of the general improvement in bone marrow function This myasthenic patient, however, had no peripheral evidence of disordered hematopoiesis He does however, have a persistently elevated sedimentation rate for which no explanation has yet been found and which is being studied Finally the low circulating eosinophil levels could not satisfactorily be explained as due to adrenal cortical hyperfunction since there was no additional evidence for this state Moreover, there appeared to be nothing unusual in the changes in urate and oxypurine metabolism and in potassium and inorganic phosphate excretion which occurred when he received ACTH For the present, therefore, the peculiarities in his hematological responses remain unexplained

DR JOHN STANBURY (Massachusetts General Hospital, Boston) We have recently studied on our Metabolic Ward a 41 year old male with moderately severe myasthenia gravis which had not responded to thymectomy 2 years before The patient was fairly well controlled on a constant daily intake of prostigmine During each of two metabolic periods during which he was given ACTH muscle strength deteriorated Upon withdrawal of ACTH at the end of the second period there was dramatic improvement to a level somewhat better than that at the beginning of the experiment

DR PAUL F A HOEFER I would like to ask Dr Torda, or anyone else who has treated patients with myasthenia gravis with ACTH, if there have been any severe attacks or fatalities We have heard of a number of such cases but only by the grapevine, and I wonder if there is any clear evidence of that

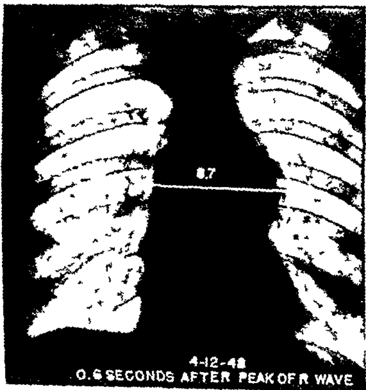
DR FREDERIC C BARTTER We have certainly seen a very severe set back We stopped giving ACTH short of fatality

DR RANDALL G SPRAGUE We had one patient with myasthenia gravis who got worse while receiving Compound E and she developed no re mission after stopping Compound E Another patient who received 100 mgs of ACTH a day for 12 days, got a little worse while receiving it, but improved after administration of ACTH was stopped How ever, she never was able to discontinue the use of prostigmine entirely

DR CLARA TORDA ACTH induced remission in every patient with myasthenia gravis in our laboratory Today ACTH is not the medica tion of choice with patients who are moribund During administra tion of ACTH patients with myasthenia gravis developed symptoms that are severe enough to endanger the life of severely ill people Some of these symptoms can however be relieved by administration of potassium

Should patients with myasthenia gravis survive administration of Cortisone without remission of myasthenia gravis this would be a con clusive proof of the hypothesis that myasthenia gravis is primarily not due to decreased secretion of Compound E by the cortex of the adrenal gland Similar conclusion may be drawn from the observation of Walker who found an increase of muscle action potential during repetitive stimulation in adrenalectomized animals instead of the decrease observed in patients with myasthenia gravis Furthermore the nature of the mild alterations of carbohydrate metabolism in myasthenia gravis does not duplicate the nature of disturbance of carbohydrate metabolism due to Compound E deficiency

DR L J SOFFER We have given ACTH to 2 patients with myasthenia gravis with thymic tumors The results obtained with the first patient were published in our original report a little over a year ago and as you recall, there occurred a marked shrinkage of the tumor associated with a considerable improvement in the clinical status of the patient The total duration of treatment with ACTH extended over a period of 4 days during which time the patient received 50 mgm daily in 4 divided doses The shrinkage of the tumor continued for approxi mately 3 weeks and the symptomatic improvement for 2 months after the 4 day period of therapy with ACTH (Fig 7) The second pa tient treated similarly failed to show any decrease in the size of the tumor and no symptomatic improvement When a thymectomy was subsequently performed on this patient the tumor was found to be surrounded by a thick fibrous tissue capsule fibers of which had ex tensively invaded the tumor parenchyma There was comparatively little cellular element present in the tumor tissue On the basis of the



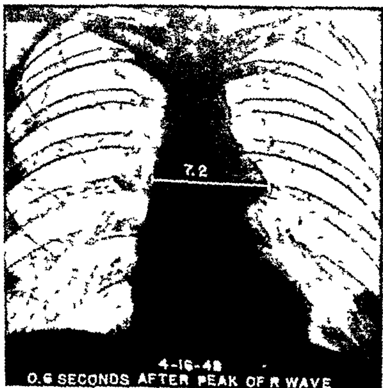


Fig 7 Roentgenograms made during the same phase of the cardiac cycle (diastole) and respiration 4-12-48 Before treatment with ACTH 4-16-48 Immediately after completion of treatment with ACTH

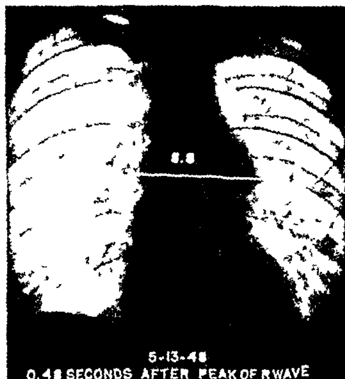


Fig 7 (continued) 5-13-48 4 weeks after completion of treatment with ACTH (From Soffer I J Gabrilove J I Laqueur H F Volterra M Jacobs M D and Sussman M L The effects of anterior pituitary adrenocorticotropic hormone (ACTH) in myasthenia gravis with tumor of the thymus *J Mt Sinai Hosp* 15 No 2 July-Aug 1948)

pathological finding it was evident why shrinkage failed to occur This patient has been followed for a year after thymectomy with no improvement in the clinical condition and no reduction in the prostigmine requirement It is possible that in addition to its therapeutic effect in myasthenia gravis ACTH may be useful in helping to determine which patients with thymic tumors may be expected to respond favorably to surgical removal Where the tumor fails to shrink appreciably following therapy with ACTH the possibility must at least be entertained that such a tumor is relatively devoid of cellular elements and hence the symptoms of the myasthenia gravis may not be particularly responsive to the surgical removal of the tumor

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The Effect of ACTH in Myotonia Atrophica and in Progressive Muscular Dystrophy

A T Milhorat

THE NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL COLLEGE AND THE RUSSELL SAGE INSTITUTE OF PATHOLOGY NEW YORK CITY

MYOTONIA ATROPHICA

The effect of ACTH was studied in 2 patients with myotonia atrophica Both patients showed muscular wasting, myotonia, testicular atrophy, creatinuria, low urinary 17 KST and diminished BMR

B B a man aged 51, received ACTH during 2 periods During the first period he was given 50 mg ACTH for 1 day and 100 mg for 7 days During the second period, 2 months later, he received 75 mg ACTH for 2 days 105 mg for 2 days 150 mg for 2 days and 125 mg for 1 day Significant observations during the first period were as follows The daily urinary excretion of 17 KST rose from the control level of 2 1 mg to 17 mg the urinary creatinine output was unaffected the creatinuria was not altered until 100 mg ACTH had been given for 4 days when the daily creatine output rose from 120 to 380 mg (Fig 1) When the administration of ACTH was discontinued the creatinuria decreased to below the pre ACTH level The excretion of urinary sodium decreased slightly during the first few days of the period and then increased slightly during the late stage of the period when ACTH was given The urinary potassium excretion was unchanged For several years the level of blood cholesterol had been high (550 to 700 mg with normal ratio of free cholesterol and cholesterol esters) and had been unaffected by various agents investigated During the pre ACTH period the concentration of cholesterol in the blood was 612 mg this level decreased until at the end of the ACTH period the level was 360 mg the total eosinophil count decreased from 103 to 3 per cmm the blood sodium level was unchanged but the blood potassium level decreased from 4 6 to 3 5 m eq L The BMR rose from −32% to −17% During the second ACTH period the creatinine output was unchanged creatinuria was not altered until the dose of ACTH had been increased to 150 mg

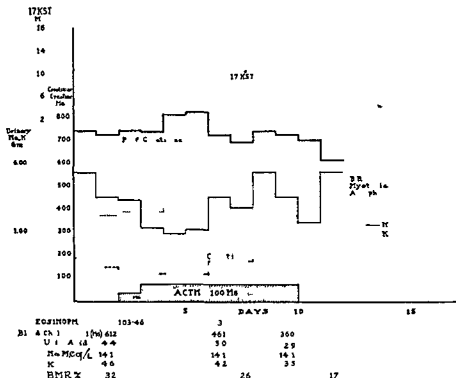


FIG 1 Effect of ACTH (Period 1) in a patient with myotonia atrophica

when the daily output of creatine increased from a level of 240 mg to levels of from 640 to 700 mg (Fig 2) On the days when 150 mg ACTH was given the urinary nitrogen was increased as much as 50% The blood cholesterol which had increased to a level of 579 mg since the termination of the first ACTH period again was decreased to 369 mg The BMR was unchanged The blood pressure was increased from a level of 124/70 to 154/76 but returned to the previous level within a few days when ACTH was discontinued

J R, a man aged 30 received 50 mg ACTH for 1 day and 100 mg daily for 7 days The total eosinophil count was decreased from 153 to 87 and the blood uric acid decreased from a level of 3 2 to 2 1 mg but no significant changes were noted in the urinary outputs of creatinine creatine potassium or 17 KST or in the concentration of chlorides urea cholesterol sodium potassium calcium or phosphorus in the blood The urinary output of potassium was increased during the first few days of ACTH administration The concentration of albumin in the blood was unchanged but that of globulin was decreased The blood pressure was increased only slightly

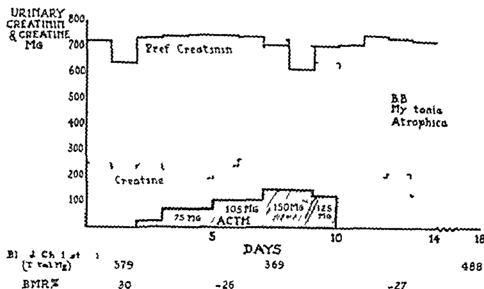


FIG 2 Effect of ACTH (Period 2) in a patient with myotonia atrophica

Although both patients recorded some subjective improvement in symptoms examinations could demonstrate no increase in muscular function during the period when the patients were in the hospital However after they returned home both patients were able to carry out their activities with less fatigue and with greater facility than previously Examination by a psychiatrist (Dr H K Hall) revealed no change in the emotional status of either patient

PROGRESSIVE MUSCULAR DYSTROPHY

ACTH was administered to 2 patients with progressive muscular dystrophy of facio scapulo humeral type

R M a woman aged 38 was maintained on a constant diet and fluid intake During a period when the daily NaCl intake was 8 gm, 40 mg ACTH daily for 2 days decreased the urinary volume to around 1000 cc for 2 days from a previous average level of 2300 cc with an increase of 3 kg in body weight This daily creatine output was increased to 475 mg for 2 days from the control level of 230 mg and then fell to a level below the control values for a period of about 9 days ACTH lowered the total eosinophil count from 103 to 10 per cmm increased the daily urinary 17 KST from 4 5 mg to 10 mg but did not affect the daily output of preformed creatinine (Fig 3) The BMR EKG AND EEG were unchanged ACTH was administered to this patient during 3 subsequent periods when the daily NaCl intake was 2 18 gm ACTH was given in amounts of 40 mg daily for 7 days 73 mg daily for 7 days and 100 mg daily for 5 days Data on the

Table 1

EFFECT OF ACTH ON AVERAGE DAILY BALANCE OF NITROGEN, CALCIUM, PHOSPHORUS, SODIUM AND POTASSIUM OF PATIENT M. M. WITH PROGRESSIVE MUSCULAR DYSTROPHY

Period	Intake					Output in Urine					Output in Feces					Balances				
	N	Ca	P	Na	K	N	Ca	P	Na	K	N	Ca	P	Na	K	N	Ca	P	Na	K
	g	mg	mg	mg	mg	g	mg	mg	mg	g	g	mg	mg	mg	g	g	mg	mg	g	mg
I Pre ACTH 8 days	9.00	1037	1211	872	2280	8.38	2[illegible]	765	530	1593	0.89	906	550	2[illegible]	365	−0.27	+105	−104	+316	+322
II 40 mg ACTH [illegible] days	9.00	1037	1211	872	2280	8.38	[illegible]	40	[illegible]	1549	0.85	836	520	29	254	[illegible]23	+132	−49	+174	+477
III [illegible] mg ACTH [illegible] days	9.00	103	1211	872	2280	8[illegible]	83	[illegible]90	485	1[illegible]22	0.73	[illegible]	61[illegible]	12	240	−0.40	−25	−91	+375	+418
IV 100 mg ACTH 4 days	9.00	1037	1211	8[illegible]2	2290	10.4[illegible]	124	[illegible]60	10[illegible]5	2470	0.67	7[illegible]0	530	24	256	−2.16	+193	+21	−247	−441
V Post ACTH 8 days	9.00	1037	1211	872	24[illegible]0	[illegible]52	50	5[illegible]5	141	1183	0.78	881	550	17	58	−0.30	+106	+66	−557	+1019
VI Post ACTH 6 days	8.80	1001	1164	840	2240	7[illegible]4	31	730	0	1347	0.83	7[illegible]8	490	17	248	+0.23	+192	−56	+103	+[illegible]45

The increased K intake was due to administered potassium citrate

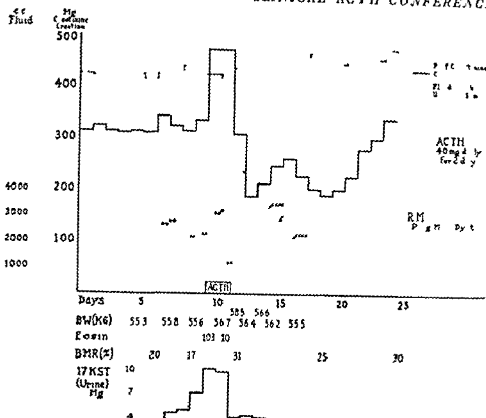


FIG 3 Effect of ACTH in a patient with progressive muscular dystrophy

complete mineral and electrolyte balance studies are shown in Table 1 The concentrations of Na and K in the blood serum were 330 mg and 17 50 mg respectively during the pre ACTH period, and 312 mg and 16 25 mg respectively after ACTH had been administered for 7 days Following further administration the blood Na level was unchanged but the concentration of K decreased to 9 0 mg % No significant changes in the outputs of creatinine or creatine were observed until 100 mg ACTH was given daily for 4 days, when the daily creatine excretion increased from a level of around 300 mg to levels of 427, 542 and 730 mg Concomitant with this increase in creatinuria the daily urinary nitrogen increased from an average level of 8 38 gm to 10 49 gm at which time the average daily nitrogen balance was −2 16 gm The average daily urinary output of 17 ketosteroids increased from 4 5 mg to around 9 mg when 75 mg ACTH was given daily when the dose of ACTH was increased to 100 mg the 17 KST output rose quickly to 20 8 mg Following cessation of ACTH therapy the 17 KST output dropped immediately to the pre

ACTH levels and remained at these levels during 4 subsequent weeks of observation The total eosinophil count was decreased about 60% When the higher doses of ACTH were given, the urine contained traces of sugar (less than 1 gram daily) The glucose tolerance test was not altered significantly The blood pressure increased from a level of 100/60 to 138/90 but returned to the former level within a few days after ACTH was discontinued

J H a man aged 19 was given 45 mg ACTH daily for 3 days,

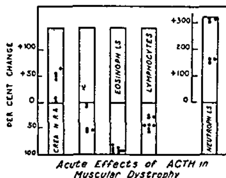


FIG 4

60 mg for 1 day and 100 mg for 4 days Urinary outputs of creatinine and creatine were not altered The body weight increased about 2 kg and the blood pressure increased from a control level of 100/74 to around 162/116 and 140 108 Within 2 days after discontinuing ACTH the blood pressure and the body weight returned to their previous values During a subsequent period the patient was studied by Dr Shorr for effects on blood pressure When ACTH was given daily in amounts of 100 mg for 4 days 150 mg for 2 days 200 mg for 3 days and 250 mg for 3 days the blood pressure levels varied from 140/92 to 108/68 The total eosinophil count which was 135 in the pre ACTH period was reduced to levels of from 32 to 18 per cmm The blood concentration of sodium was unchanged but that of potas sium was decreased from 15 9 mg to 13 7 mg The urinary output of creatinine was not altered but the daily elimination of creatine which was unaffected by ACTH in doses up to 150 mg daily increased by values of from 100 to 200 mg when the dosage of ACTH was increased to 200 and 250 mg daily The BMR was unchanged The carbo hydrate metabolism was unchanged Evaluation of muscular dis- ability throughout the course of studies and during the subsequent period gave no evidence of increase in muscular function However the effect of ACTH in progressive muscular dystrophy of pseudohyper-

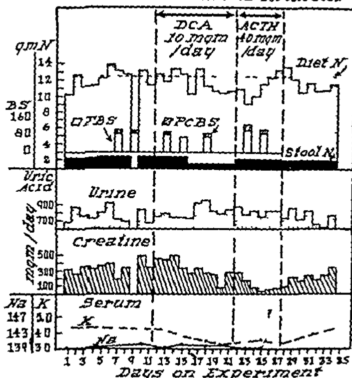


Fig 5

trophic type remains to be investigated the 2 patients who were studied had muscular dystrophy facio scapulo humeral type

DISCUSSION

DR FRANK H TYLER We have performed 9 ACTH response tests in 7 boys with childhood dystrophy In this group we have seen a consistent immediate elevation in urinary creatine (Fig 4) In a patient with rheumatoid arthritis and creatinuria treatment with 40 mgm per day of ACTH reduced the creatinuria to an insignificant amount (Fig 5) We have obtained very confusing results as far as uric acid excretions are concerned in dystrophy (Fig 4) However, in 4 of them there was a significant fall averaging about 50% in uric acid excretion instead of an increase

We have treated one childhood dystrophy with small doses of ACTH for a 9 day period with no symptomatic change and no evidence of change in muscle function

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A Clinical Study of the Effect of ACTH on Chronic Neurologic Disorders in Seven Patients

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This report deals with a brief clinical screening of the effect of ACTH (Armour) on 4 types of chronic neurologic disorders in 7 patients at the Neurological Institute of New York in August and September 1949 The purpose of this experiment was to ascertain whether or not a markedly beneficial response could be obtained within a limited time and to determine the advisability of more detailed study of these clinical entities Evaluation was based on clinical observations

The group was comprised of 2 patients with multiple sclerosis two with Parkinson s syndrome one with amyotrophic lateral sclerosis one with progressive muscular atrophy and one with progressive muscular dystrophy Armour ACTH in doses of 25 mgm to 75 mgm intramuscularly 4 times daily was given with total dosages ranging from 700 mgm to 2575 mgm over periods of from 5 to 17 days The lowest daily dose was 100 mgm the highest 300 mgm No local reactions to the drug were noted The pertinent findings in each case will be briefly presented

T S, Female Age 60

Arteriosclerotic parkinsonism of 1½ years duration with involvement of the right upper and occasionally the right lower extremities Unchanged during the 6 months prior to hospitalization

Findings 1 Diminished swing of right upper extremity and associated movements of trunk on walking

2 Moderate rigidity with cogwheel phenomenon in right upper extremity mild rigidity in other extremities

3 Coarse rhythmic alternating tremor in right hand and upper

extremity with pill rolling movements of fingers of right hand at rest
4 Verbalization slightly slow and monotonous
5 Mild masking of facies
No appreciable change in the above findings was apparent after 700 mg of ACTH in 5 days
Following the course of ACTH, the patient noted increase in rigidity and tremor as well as some generalized weakness She was emotionally upset The exacerbation of signs and symptoms cleared over a 7 day period
Follow up report 6 weeks after ACTH reveals no significant change from her baseline status

L D, Male, Age 59

Post encephalitic parkinsonism of 5 years duration No appreciable change in rigidity and tremor during the past four years
Findings 1 Masked facies
2 Diminished associated movements more marked in right upper extremity while walking
3 Coarse rhythmic alternating tremor of right upper extremity with pill rolling movements of fingers of right hand
4 Moderate rigidity of all extremities particularly on right with cog wheel phenomenon in right upper extremity
Examination after ACTH 1200 mg administered during a period of 7 days revealed no change in the patient's neurologic status No untoward systemic reaction

J A, Male, Age 38

Progressive muscular atrophy with twitching of muscles of arms and shoulders first noted 1 year before admission Progressive weakness of hands particularly thumbs for 2 months
Findings 1 Multiple fasciculations in upper and lower extremities
2 Mild atrophy of deltoids, biceps, triceps and first dorsal interosseous muscles bilaterally
3 Hand grip tested by momentarily squeezing rolled up blood pressure cuff inflated to 20 mm Hg left 236 mm Hg, right 184 mm Hg Shoulder girdle and upper extremity muscle strength estimated to be 80% of normal
Patient accidentally incurred lacerations of right hand after receiving 500 mg ACTH in 4 days Grip tested in above manner, left 202 mm Hg right 192 mm Hg prior to this incident
Examination after a 9 day course of ACTH 1800 mg revealed
1 Equivocal reduction in fasciculations
2 Mild atrophy as before
3 Hand grip tested with rolled up blood pressure cuff inflated to

20 mm Hg left 198 mm Hg right could not be tested Shoulder girdle and upper extremity strength essentially unchanged

Follow up examination 2 weeks later showed a marked increase in fasciculations No significant change in muscle power

Baseline creatine excretion 197 mg /24 hours, creatinine 1065 mg /24 hours (24 hour urine volume 650 cc)

After 9 day 1800 mg ACTH course creatine excretion 469 mg / 24 hours creatinine 1377 mg /24 hours (24 hour urine volume 3720 cc)

C E , Male, Age 43

Amyotrophic lateral sclerosis with weakness in the hands and upper extremities first noted 3 months prior to admission with progressive weakness and stiffness of the lower extremities huskiness of voice difficulty in articulation and swallowing Rheumatic heart disease inactive, compensated

Findings 1 Spastic gait with audible shuffling

2 Moderate atrophy of the intrinsic muscles of the hands arms and shoulder girdle bilaterally

3 Multiple fasciculations in the upper and lower extremities

4 Weakness manifested by—

a) an estimated 60% of normal muscle power in shoulder girdle and upper extremity musculature

b) grip tested by momentary squeezing of rolled up blood pressure cuff inflated to 20 mm Hg left 168 mm Hg right 162 mm Hg ,

c) inability to raise from supine to sitting position unaided by arms

5 Hyperactive deep reflexes from jaw jerk down Superficial abdominals normal Bilateral transient ankle clonus Bilateral Babinski signs

6 Voice soft, husky and monotonous

Examination after ACTH 1900 mg over a period of 10 days

1 Gait less spastic without audible shuffling

2 Atrophy as previously noted

3 Fasciculations 80% decreased

4 Weakness manifested by—

a) an estimated 75% of normal muscle power in shoulder girdle and upper extremity musculature

b) grip tested with blood pressure cuff inflated to 20 mm Hg left 160 mm Hg right 150 mm Hg and

c) able to rise from supine to sitting position unaided by arms

5 Reflexes clonus and Babinski signs as before

6 Voice strong and clearer but still monotonous

Re evaluation after 2 days without ACTH revealed the patient

to have coryza without temperature elevation Fasciculations were markedly increased Increased spasticity of gait with audible shuffling noted

An additional 675 mg of ACTH was administered over a period of 5 days with apparent 50% decrease in fasciculations over the pre ACTH observation Gait less spastic without audible shuffling Shoulder girdle and upper extremity weakness estimated 60% of normal Able to rise from supine to sitting position unaided by arms but only with lower extremities held down by examiner Grip tested with rolled up blood pressure cuff inflated to 20 mm Hg left 180 mm Hg, right 200 mm Hg Remainder of examination unchanged

Follow up examination 2 weeks after last ACTH revealed a marked increase in generalized fasciculations audible shuffling spastic gait, and weakness approximately the same as at termination of ACTH administration

Baseline creatine excretion 129 mg /24 hours creatinine 1627 mg 24 hours (24 hour urine volume 2064 cc) After 1900 mg ACTH in 10 days—creatine excretion 22 mg /24 hours creatinine 1778 mg /24 hours (24 hour urine volume 3600 cc)

M H , Female Age 20

Multiple sclerosis with onset 7 months prior to admission One mild remission for 2 months ending 7 weeks before hospitalization Condition unchanged since

Findings 1 Unable to walk without assistance Gait ataxic, broad based and spastic

2 Unable to stand unsupported with feet together With feet 12 inches apart unsteady with eyes open falls forward with eyes closed

3 Rhythmic head tremor

4 Bilateral extremity intention tremor

5 Deep reflexes hyperactive No abdominals Bilateral Babinski signs

6 Dysarthria

7 Nystagmus

8 Ptosis (1/3rd closure) left eyelid

9 Moderate euphoria

ACTH 1300 mg in 8 days discontinued because of drowsiness and 3 days progressive bradycardia from 76/min to 48/min Electrocardiogram at this time read as probably within normal limits T_4F borderline low in amplitude Serum potassium 3 4 meq/1, sodium 139 meq 1 (flame photometer)

Examination 1 Able to walk across the ward, turn and come back unassisted Gait wide based but less ataxic and spastic than on base line examination

2 Can stand for at least 30 seconds with feet together eyes open and closed

3 Head tremor markedly decreased in excursion

4 Minimal terminal tremor of hands and feet on volitional movement

5 Deep reflexes no longer hyperactive Abdominals elicited minimally twice on either side Bilateral Babinski signs

6 Speech more fluent less dysarthric

7 Nystagmus as before

8 Ptosis left eyelid (⅓th closure)

9 Euphoria increased

Drowsiness decreased and pulse rose to 74/minute 19 hours after last 75 mg dose ACTH 100 mg/day resumed after a 2 day interval Remainder of neurologic status unchanged

After ACTH 600 mg in 5 more days the improvement in gait and equilibrium was slightly less apparent than at the end of the first 8 days Other signs of improvement were essentially the same as noted at the termination of the first course

Follow up report 2 weeks later revealed the patient s tremor gait and equilibratory disturbance to have returned to approximately the pre ACTH intensity

Cerebrospinal Fluid Studies Baseline CSF WBC 3/mm³ protein 61 mg %, gamma globulin 7 8 mg % (13% of total protein) colloidal gold 0, Kolmer negative After ACTH 1300 mg in 8 days CSF WBC 4/mm³, protein 32 mg % gamma globulin 4 1 mg % (13% of total protein)

C G, Female, Age 37

Multiple sclerosis with onset 7 years before present hospitalization A marked partial remission until 18 months prior to admission since which time she has become progressively worse

Findings 1 Unable to walk without assistance Gait ataxic and broad based

2 Unable to stand alone with feet apart and eyes open

3 Head and right upper extremity tremor both made worse on volitional movement

4 Bilateral cerebellar signs

5 Mild right hemiparesis

6 Dysarthria

7 Deep reflexes hyperactive Absent abdominals No clonus Bilateral Babinski signs

8 Nystagmus

9 Ptosis (¼th closure) left eyelid

10 Mild euphoria

Examination after ACTH 1600 mg in 9 days—

1 Able to walk at least 3 yards without assistance

2 Gait ataxic and broad based

3 Can stand unsteadily alone with feet 6 inches apart, eyes open and closed

4 Head and right upper extremity tremor slightly increased over baseline examination

5 Cerebellar signs as before

6 Mild right hemiparesis

7 Dysarthria

8 Slight increase in deep reflex hyperactivity Transient ankle clonus Bilateral Babinski signs

9 Nystagmus

10 Moderate euphoria

Follow up 2 weeks later revealed the patient to be unable to stand or walk unassisted Remainder of examination as on discharge

Cerebrospinal Fluid Studies Baseline CSF Cells 8/mm³, protein 75 mg % gamma globulin 19 mg % (25% of total protein), colloidal gold 3233311000 Kolmer negative After ACTH 1600 mg in 9 days, CSF WBC 9/mm³, protein 29 mg %, gamma globulin 10 9 mg % (38% of total protein)

E M , Female, Age 23

Progressive muscular dystrophy with biopsy confirmation of 4 years duration

Findings 1 Waddling gait with mild steppage component

2 Flabbiness and decreased substance of shoulder girdle and arm musculature Rubbery hypertrophy of both calves

3 Muscle weakness manifested by—

a) arising from prone position by climbing movements of upper extremities

b) difficulty in arising from chair,

c) unable to abduct upper extremities more than 30° or maintain them even momentarily against gravity,

d) hold forward extended upper extremities 30° elevated for 12 seconds

e) hand grip tested with rolled up blood pressure cuff inflated to 20 mm Hg momentarily increased left 74 mm Hg, right 56 mm Hg

Examination after ACTH 1800 mg administered over a period of 11 days—

1 Gait slightly less waddling Steppage component same

2 Muscle status unchanged

3 Muscle weakness—

a) climbs from prone to kneeling position as on initial examination

b) slightly less difficulty in arising from chair

c) unable to abduct upper extremities more than 30° but can maintain this position against gravity for 18 seconds

d) hold forward extended upper extremities 45 elevated for 36 seconds

e) hand grip tested as above left 184 mm Hg right 150 mm Hg

Follow up report 6 weeks post ACTH revealed no remarkable change

Baseline creatine excretion 583 mg /24 hours creatinine 544 m/24 hours (24 hour urine volume 835 cc)

After ACTH 1800 mg in 11 days creatine excretion 570 mg /24 hours creatinine 488 mg /24 hours (24 hour urine volume 860 cc)

Fig 1 summarizes the laboratory data of the cases studied

CONCLUSIONS

1 No markedly beneficial results were obtained

2 The alteration of the neurologic status concomitant with ad

N	Case	Diagnosis	Eos nephil ount befor CT pe m 3	Eosinoph cou hr er 1 26mg ose ACT	Eosinophile oun per ent f l	E S R mm hr W ergren be or CT	D tion f ourse (d)	T l do CT q	Subj feeling well being	Flushing of face	Weight q (lb)	R sult
1	T S F 9 60	Arteriosclerotic Parkinsonism	41	5	68	12	5	700	0	+	2.5	0
2	L D M 9 59	Postencephalitic Parkinsonism	151	31	79	10	7	1200	0	0		0
3	J A M age 38	Progressive Muscular At phy	54	15	72	2	9	1800	+	+	5.25	0
4	C E 9 43	Amy trophic eral Sclerosis	104	77	26	5	17	2575	+	+	9	
5	M H F 9 20	M ltiple Scle osis	75	6	92	10	15	800	+	+		+
6	C G F 9 37	Multiple Sclerosis	190	58	70		9	600	0		6	0
7	E M F 9 23	Progressive M lar Dys ophy	100	47	53	38	11	800	+	gr	3.25	

Fig 1

ministration of ACTH in one relatively early case of multiple sclerosis and a rapidly progressive case of amyotrophic lateral sclerosis indicates that further investigation is desirable

3 No serious untoward clinical reactions were observed in 7 patients with neurologic diseases on relatively high doses of ACTH

DISCUSSION

DR C H TRAEGER I should like to emphasize one point I don t think we brought out sufficiently

In almost all of these 7 patients with these chronic neurological diseases we gave as much as 300 mgs of ACTH a day for 3 days, with no ill effects

Summary

John R Mote

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It may be worthwhile to summarize in general form the volume of work done and the number of diseases and patients studied during the investigations contributing to this volume since a truly colossal amount of investigation has been accomplished during the past three years The data to follow have been collected from information obtained from the members of the Conference Although it is not precise to the last detail, I would estimate that it is correct to plus or minus 10% of the figures shown

Fig 1 is an overall chart of the general categories of patients studied and the number of patients investigated in each group It is interesting to note that a total of 53 normal human beings and 73 human beings with various endocrine abnormalities have been studied Practically all of these subjects were on one or another type of complete metabolic balance study and naturally these two groups constituted the bulk of the work done during the first two years that ACTH has been available

The other general categories of diseases in this chart cover a wide range and the studies conducted varied widely both in different syndromes and in different institutions They include not only established complete metabolic studies but also various other investigations aimed at detecting metabolic shifts of one type or another

Normals	53
Endocrine Abnormalities	73
Collagen Diseases	214
Hypersensitivities	38
Infections	43
Malignancies	24
Mental Disease	70
Muscle Demyelinating Diseases	16
Miscellaneous Diseases	82
	613

FIG 1

Fig 2 gives a breakdown of the endocrine abnormalities studied It is interesting that the bulk of the commonly encountered endocrine dysfunctions have been studied and practically all of them constituted metabolic investigations of varying types aimed at clarifying the interrelationships of the adrenal gland to the other glands of internal secretion

Normals	53
Endocrine Abnormalities	
Panhypopituitarism	18
Acromegaly	4
Diabetes Insipidus	1
Addison s Disease	6
Adrenal Hyperplasia	20
Hypothyroidism	13
Hyperthyroidism	13
Congenital Hypoglycemia	9
Pre-diabetic State	6
Diabetes	4
Ovarian Agenesis	2
Female Castrates	1
Male Castrates	2
Ovarian Luteinization with Virilism	1
	73

Fig 2

Fig 3 is a breakdown of the various collagen diseases that have been under investigation You will note that the definition of these diseases is, to say the least *loose*, in that ulcerative colitis, iritis and interstitial keratitis have been included On the other hand, in the light of the results obtained by the members present, to date, this definition may be quite as good as some of the more orthodox definitions that have been put forth in the past

Collagen Diseases	
Rheumatoid Arthritis	128
Juvenile Rheumatoid Arthritis	4
Rheumatic Fever	25
Disseminated Lupus Erythematosus	24
Dermatomyositis	9
Scleroderma	7
Periarteritis Nodosa	4
Psoriatic Arthritis and Psoriasis	5
Ulcerative Colitis	4
Regional Ileitis	1
Acute Iritis	2
Interstitial Keratitis	1
	264

Fig 3

It is rather natural that rheumatoid arthritis should constitute the largest single number of cases in this group in view of both the publicity and pressure concerning this disease. On the other hand, it is surprising that as many as 24 cases of disseminated lupus erythematosus have been studied since this is not normally considered a very common disease. The rest of the diseases in this chart are simply to fill out those studied by the members present.

Fig. 4 outlines the various types of malignancies that have been studied during the past 3 years. You have already heard some of the results obtained in the lymphomas. In general, it may be said the only malignancies in which adrenal gland stimulation has had a clear-cut effect are the lymphomas and leukemias.

Malignancies	
Acute Lymphatic Leukemia	2
Chronic Lymphatic Leukemia	7
Hodgkins Disease	2
Lymphosarcoma	1
Lymphoma	1
Ewing's Tumor	1
Mycosis Fungoides	1
Carcinoma of Breast	4
Carcinoma of Prostate	2
Sarcoid	2
Bronchogenic Carcinoma	1
	24

FIG. 4

Fig. 5 is simply a breakdown of the mental diseases studied and you have already heard the results obtained in these studies. It is obvious from the data presented in this volume that considerable work will be required in this complex field before the role of the adrenal gland in these syndromes can be clearly elucidated.

Mental Disease	
Acute Alcoholism	11
Chronic Alcoholism	2
Schizophrenia	12
Depression	8
Anxiety State	35
Postpartum Psychosis	1
Insomnia	1
	70

FIG. 5

Fig 6 is a breakdown of the various types of hypersensitivities and infections that have been studied In view of the clear cut results obtained in this field and the fundamental character of the issues involved, it is clear that additional serious studies must be undertaken The lower part of this figure summarizes the infections studied Here again the fundamental aspects of this area of medicine require detailed investigation

Hypersensitivities	
Asthma	15
Hay Fever	7
Atopic Dermatitis	2
Migraine	2
Drug Sensitivity	3
Pemphigus	5
Exfoliative Dermatitis	1
Loeffler s Syndrome	3
	38
Infections	
Pulmonary Tuberculosis	2
Poliomyelitis	35
Acute Viral Hepatitis	2
Chronic Viral Hepatitis	1
Lobar Pneumonia	2
Viral Pneumonia	1
	43

Fig 6

Fig 7 is simply a breakdown of the muscle dystrophies and demyelinating diseases that have been studied The results, as you already know are not clear cut

Muscle and Demyelinating Diseases	
Progressive Muscular Dystrophy	5
Myotonia Atrophica	3
Multiple Sclerosis	2
Amyotrophic Lateral Sclerosis	2
Parkinsonism	2
	14

Fig 7

Fig 8 is a breakdown of what has been classed as ' miscellaneous diseases some of which have been reported in detail and some have not It may well be that gout should probably fit into the group of endocrine dysfunction

Miscellaneous	
Gout	32
Hypertension	6
Nephritis	4
Nephrosis	21
Alcoholic Cirrhosis	2
Malnutrition	12
Hypoproteinemia	2
Hemolytic Anemia	2
Idiopathic Anemia	1
	82

Fig 8

In summary extensive studies of the effect of ACTH in human beings over the past 3 years are reflected in the contents of this volume It is obvious from the results presented that a tremendous amount of investigation will be required over a wide area of medicine before a reasonable pattern of the role of the adrenal gland in health and dis ease can be brought forward